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PhD Thesis

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Effect of early initiated high-intensity, aerobic exercise in patients with lacunar stroke

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Title and subtitle:	Effect of early initiated, high-intensity, aerobic exercise in patients with lacunar stroke
Topic description:	Lacunar stroke is characterised by short-lasting symptoms. Although these patients are at high risk of recurrent stroke, they are rarely offered exercise interventions following hospital discharge. Whether home-based high-intensity interval training will improve cardiorespiratory fitness is not known, and neither have the level of physical activity pre-stroke been described in patients with lacunar stroke.
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Front page illustration:	A hard working brain doing high-intensity interval training, illustrated by Per Husum.

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Abbreviations

ACSM	American college of sports medicine
ADC	apparent diffusion coefficient value
AHA/ASA	American heart association/American stroke association
AI	augmentation index
ANCOVA	analysis of covariance
AX3	Axivity, accelerometer to assess physical activity
BMI	body mass index
BP	blood pressure
COPD	chronic obstructive pulmonary disease
CERT	consensus on exercise reporting template
CI	confidence interval
cLDA	constrained longitudinal data analysis
CONSORT	consolidated standards of reporting trials
CT	computed tomography (scan)
CVD	cardiovascular disease(s)
DM	diabetes mellitus
DWI	diffusion weighted imaging
FLAIR	fluid attenuated inversion recovery
HDL	high density lipoproteins
GCT	graded cycling test
GCT- TT	graded cycling test with talk test
GRRAS	Guideline for reporting reliability and agreement studies
HIIT	high-intensity interval training
HR	heart rate
HRR	heart rate reserve
HsCRP	high sensitivity c-reactive protein
Hz	hertz
ICAM-1	intercellular adhesion molecule 1
ICC	intraclass correlation coefficient
IL-6	interleukin-6

IQR	interquartile range
LDL	low density lipoproteins
LIPA	lipoprotein(a)
MDI	major depression inventory
MET	metabolic equivalent of task
MFI-20	multidimensional fatigue inventory
MICE	moderate-intensity continues training
µg/ml	microgram per millilitre
mmHg	millimetres of mercury
mmol/L	millimoles per litre
MoCA	Montreal cognitive assessment
MRI	magnetic resonance imaging
ng/ml	nanogram per millilitre
NIHSS	national institutes of health stroke scale
nmol/L	nanomoles per litre
PAS2	physical activity scale (version 2.1)
pg/ml	picogram per millilitre
pmol/L	picomoles per litre
PPS	pressure pain sensitivity
Pro-ADM	pro-adrenomedullin
Pro-ANP	pro-atrial natriuretic peptide
RHI	reactive hyperaemia index
RPE	rating of perceived exertion
Rpm	rounds per minute
SD	standard deviation
SEM	standard error of measurement
SEM_{95}	standard error of measurement with 95% confidence interval
SF-36	health status questionnaire short-form 36
SPIRIT	standard protocol items: recommendations for interventional trials
SRD	smallest real difference
SSS	Scandinavian stroke scale
STROBE	strengthening the reporting of observational studies in epidemiology

TIA	transient ischemic attack
TNF	tumour necrosis factor
TOAST	trial of ORG 10172 in acute stroke treatment (classification of sub types of ischemic stroke)
TT	talk test
TT-	the level of exercise intensity where the patients is no longer able to speak comfortably
TUG	timed up and go test
US	United States
VCAM-1	vascular cell adhesion molecule 1
VEGF	vascular endothelial growth factor
VO_{2max}	maximal oxygen consumption
W	watt(s)

Definitions

Aerobic exercise/ aerobic physical activity	"Activity in which the body's large muscles move in a rhythmic manner for a sustained period of time. Aerobic activity, also called endurance or cardio activity, improves cardiorespiratory fitness. Examples include brisk walking, running, swimming, and bicycling" (1).
Cardiorespiratory fitness	"A health-related component of physical fitness. The ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity. Usually expressed as measured or estimated maximal oxygen uptake (VO2max)" (2).
Exercise	"A subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective. "Exercise" and "exercise training" frequently are used interchangeably and generally refer to physical activity performed during leisure time with the primary purpose of improving or maintaining physical fitness, physical performance, or health" (2).
Physical activity	"Any bodily movement produced by skeletal muscles that requires energy expenditure" (2)

Preface

This thesis is based on one method-study, one trial paper and two papers reporting results from the trial. All studies were conducted at the Stroke Unit, Department of Neurology, Herlev Gentofte Hospital, between November 2014 and April 2018. The data on which the four papers are based, have been collected by Rikke Steen Krawcyk (RSK) and all patient inclusions were solely done by RSK.

With a strong interest to reduce the impact of stroke and the risk of recurrent stroke we have focused on the patients suffering from a lacunar stroke associated to small artery occlusion. These patients often display mild symptoms and fast spontaneous recovery and are thus not considered candidates for rehabilitation or exercise interventions following their hospital discharge. However, it is known that patients with lacunar stroke have a three-fold increased risk of recurrent stroke and a high risk of cognitive decline and dementia (3). Therefore, we wished to investigate a possible preventive effect of an early initiated aerobic exercise intervention in this patient group. A major focus of this thesis was to identify an exercise program that was feasible and easy to implement in the daily clinical practise and in the daily living routine for individuals at risk of cerebrovascular disease. This initiation of exercise routines was of particular interest, as previous studies have shown that both a higher level of physical activity and a higher cardiorespiratory fitness (VO_{2peak}) are associated with a reduced risk of stroke (4-7). Furthermore, we wanted to identify an easy, reproducible, bedside-side outcome measure, by which it was possible to assess the degree of cardiorespiratory fitness in the patients both inside the hospital and in various rehabilitation settings without involvement of heart rate measurements. Because, the latter we consider a major issue in evaluation of cardiorespiratory fitness as 20–30% of patients who experienced a stroke, the heart rate variability may be caused by autonomic dysfunction or atrial fibrillation, and treatment with antihypertensive and heart regulatory medication, such as beta-blockers modulates heart rate response during exercise (8). The Talk Test (TT) is applied in cardiac rehabilitation to evaluate and guide exercise intensity following a cardiovascular event (9) but it was not known if this outcome measure was applicable in patients with lacunar stroke. In this thesis, firstly we performed a reliability study, investigating relative reliability (ICC values) and absolute reliability (measurement error) of the Graded Cycling Test with Talk Test (GCT-TT) in patients with lacunar stroke. Secondly, we hypothesised that patients with lacunar stroke live a sedentary lifestyle prior to their stroke and that they potentially will continue this lifestyle after

hospital discharge. Therefore, we evaluated baseline values from "The effect of aerobic exercise in patients with lacunar stroke" and evaluated pre-stroke physical activity and post-stroke health profile in patients with lacunar stroke. Finally, we conducted a randomised controlled trial (RCT) to examine the effect of home-based high-intensity interval training for 12 weeks in addition to usual care on cardiorespiratory fitness, general well-being and biomarkers. This patient cohort will be followed for a 5-year period post-stroke to evaluate adherence to training and rate of cerebrovascular events. The follow-up visits at 6 and 12 months post-stroke will evaluate long-term adherence to physical activity. Subsequently, yearly follow-up using patient records, questionnaires, and registers (The Danish National Patient Registry and The Danish Stroke Registry) will be done to evaluate number of incidence of cerebrovascular events (recurrent stroke) or death. Only data from the baseline and post-intervention assessment is included in the thesis as the follow-up is on-going.

This thesis is based on the following four papers:

1. Steen Krawcyk R, Vinther A, Caesar Petersen N, Kruuse C. "Graded Cycling Test with Talk Test" Is a Reliable Test to Monitor Cardiovascular Fitness in Patients with Minor Stroke. J Stroke Cerebrovasc. Dis. 2017;26(3):494-9.
2. Rikke Steen Krawcyk, Anders Vinther, Nicolas Caesar Petersen, Jens Faber, Rasmus Hvass Hansen, Egill Rostrup and Christina Kruuse. "Home-based aerobic exercise in patients with lacunar Stroke: design of the HITPALS randomized controlled trial" Contemporary clinical trial communication, accepted, 2019.
3. Rikke Steen Krawcyk, Anders Vinther, Nicolas Caesar Petersen, Jens Faber, Helle K Iversen, Thomas Christensen, Christina Kruuse. "Self-reported physical activity and health profile in patients with lacunar stroke". Submitted to Journal of stroke and cerebrovascular diseases.
4. Rikke Steen Krawcyk, Anders Vinther, Nicolas Caesar Petersen, Jens Faber, Helle K Iversen, Thomas Christensen, Shazia Rehman, Tobias Wirenfeldt Klausen, Kate L. Lambertsen, Egill Rostrup, Christina Kruuse. "Effect of home-based high-intensity interval training in patients with lacunar stroke: a randomized controlled trial". Submitted to Frontier in neurology.

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Thesis at a glance

	Question	Methods	Results	Conclusion
I	What is the reliability and measurement error of 'The Graded Cycling Test with Talk Test'(GCT-TT) in patients with lacunar stroke?	A test-retest study. The test is performed twice a day, separated by 1-hour rest period Cycling at a stationary bicycle with gradually increased workload (15 W), reciting a text passage every minute. Test stops when the patient is no longer able to speak comfortably	• 60 patients included • High test-retest reliability ($ICC_{2.1}$: 0.97 [0.95-0.98] • Minor measurement error (SEM_{95}: 12.9 W, and SRD: 18.3 W)	• The GCT-TT is feasible and reliable for monitoring exercise effect in patients with lacunar stroke • The high reliability and small measurement error makes it a valuable outcome measurement in clinical practice
III	Do patients with lacunar stroke adhere to the recommendations on physical activity pre-stroke? and are there any associations between pre-stroke physical activity and stroke risk factors?	An evaluation of baseline-values from the HITPALS -study assessing: self-reported pre-stroke physical activity and describing potential associations between pre-stroke physical activity and risk factors for stroke: age, sex, education, pre-existing diabetes, BMI, cardiorespiratory fitness, history of hypertension, and lipids	• 79% of our patients adhered to the minimal recommendations on physical activity, pre-stroke • 35% performed vigorous-intensity activity, pre-stroke • Pre-stroke physical activity correlated with history of hypertension and male sex	• Our patients had a similar level of physical activity as the general Danish adult population • Only 35% performed physical activity with an exercise intensity sufficient to improve cardiovascular fitness • To reduce risk of stroke, higher intensity of activity may be warranted
II & IV	What is the effect of home-based high-intensity interval training (HIIT) for 12 weeks post-stroke in addition to usual care versus usual care only?	Study II: Study-protocol Study IV: Randomized controlled trial Evaluation of the effect of home-based HIIT on cardiorespiratory fitness (primary outcome), physical activity, body mass index, endothelial function, blood pressure, stress, cognition, fatigue, depression, well-being, and blood biomarkers	• 71 patients were included with 63 patients completing the study • No significant difference was detected between the groups in cardiorespiratory fitness, general well-being or in biomarkers. • Relatively many patients in the intervention group increased their time spent on vigorous-intensity exercise noticeably	• Home-based HIIT was feasible and safe in patients with lacunar stroke but without a translation of effect on cardiorespiratory fitness, general well-being or biomarkers within 12 weeks • Further investigations on long-term effect of home-based HIIT and possible ways to improve cardiorespiratory fitness after lacunar stroke are warranted

Summary

Stroke is one of the leading causes of acquired disability worldwide and nearly 12,500 individuals suffer from a stroke each year in Denmark. Approximately one fourth of all ischemic strokes are defined as small artery occlusion also termed lacunar stroke. The treatment includes medication for secondary prevention and advice on self-managed modifiable risk factors, including physical activity. Evidence supports cardiorespiratory fitness as part of the stroke rehabilitation to improve everyday activities and to prevent cardiovascular diseases. There are several barriers for patients to engage in physical activity following a stroke, including environmental and personal barriers. It may take more than regular encouragements and verbal instructions on physical activity to change habits, the type of exercise may play a role in initiation and adherence. High-intensity interval training may be feasible, time-effective, and cost-effective in both rehabilitation and secondary prevention after stroke in patients with lacunar stroke who present with minor or no long-term deficits.

We conducted a methodological study to examine reliability and measurement error of the Graded Cycling Test with Talk Test (GCT-TT) in patients with lacunar stroke. We found that the GCT-TT was reliable to monitor the effect of exercise and had minor measurement error (study I). Furthermore, we hypothesised that patients with lacunar stroke had a sedentary behaviour prior to stroke as inactivity is one of the greatest risk factors for stroke. Thus, we evaluated baseline values from our randomised controlled trial (RCT) (Effect of home-based high-intensity interval training in patients with lacunar stroke, HITPALS-study to identify the pre-stroke physical activity and potential associations between pre-stroke physical activity and stroke risk factors (study II). In total, 79% of the included patients adhered to the international minimum recommendation on physical activity pre-stroke, corresponding to the level seen in the general Danish adult population. However, only 35% of the patients did vigorous-intensity activity prior to stroke (study III). Finally, in an RCT we compared the effect of 12-weeks home-based high-intensity interval training in addition to usual care in patients with lacunar stroke, versus usual care only, on cardiorespiratory fitness, general well-being, endothelial function and biomarkers. In conclusion, additional home-based HIIT initiated within three weeks from their stroke was feasible and safe for patients with lacunar stroke. We succeeded in motivating more patients in the intervention group to be physically active with vigorous-intensity activity and spending more time on vigorous-intensity activity than in the usual care group. However, this increased activity from baseline to

the post-intervention assessment was not translated into an effect on cardiorespiratory fitness, general well-being, endothelial function or in biomarkers. Future results will reveal if the intervention had any long-term effect or if more intensive exercise is warranted for a cardiovascular effect and risk of re-stroke or cognitive decline in this patient group.

Dansk resumé

Slagtilfælde er en af de hyppigste årsager til erhvervet hjerneskade i verden og hvert år rammes ca. 12.500 danskere af et slagtilfælde. 25% af alle iskæmiske slagtilfælde skyldes småkars-sygdom (små blodpropper) i hjernen. Den primære behandling er forebyggende medicin og selvregulerende livsstilsændringer, herunder fysisk aktivitet. Forskning viser, at konditionstræning efter slagtilfælde fremmer patienternes daglige funktionsevne, ligesom det også forebygger udviklingen af hjerte-kar-sygdom. Der er forskellige årsager til, at fysisk aktivitet i hverdagen kan være svært for patienter med slagtilfælde, herunder udfordringer med at færdes i de fysiske omgivelser eller personlige udfordringer. Regelmæssig vejledning og mundtlige informationer ser ikke ud til at være tilstrækkeligt til at få patienterne til at ændre trænings vaner, der skal fysiske handlinger til. Høj-intensitets træning er en træningsform som er gennemførbar i både hospital- og kommunalt regi. Det er en tidsbesparende og en billig genoptræningsform efter slagtilfælde til at generhverve eller opretholde hverdagsaktiviteter og forebygge hjerte-kar-sygdom – måske denne træningsform er brugbar til patienter med småkars-sygdom.

Vi gennemførte først et metodestudie, som undersøgte reliabilitet og måleusikkerheden af konditionstesten ”Graded Cycling Test with Talk Test” (GCT-TT). Studiet viste, at testen var reliabel til at undersøge træningseffekten hos patienter med småkars-sygdom, og at testen havde en minimal måleusikkerhed (manuskript I). Yderligere havde vi en hypotese om, at patienter med småkars-sygdom lever en inaktiv tilværelse før deres blodprop, idet fysisk inaktivitet er en af de hyppigste risikofaktorer for slagtilfælde. Derfor evaluerede vi baseline-værdierne fra studiet: ”Effekt af hjemmebaseret høj-intensitets træning til patienter med småkars sygdom (HITPALS-studiet)” (manuskript II), som havde til formål at undersøge patienternes fysisk aktivitetsniveau før deres slagtilfælde. Yderligere undersøgte vi, om der var en sammenhæng mellem det fysiske aktivitetsniveau før slagtilfældet og risikofaktorer for blodprop. Vi fandt, at 79% af de inkluderede patienter levede op til anbefalingerne for fysisk aktivitet, og at deres fysiske aktivitetsniveau var på niveau med den generelle danske befolkning. Dog var det kun 35% af patienterne, som udøvede hård fysisk træning før deres slagtilfælde (manuskript III). Til sidst gennemførte vi et RCT, som undersøgte effekten af 12 ugers høj-intensitets træning hjemme til patienter med småkars-sygdom versus sædvanlig behandling. Studiet viste, at det var sikkert og gennemførbart at træne tidligt i efterforløbet for patienter med småkars-sygdom. Desuden lykkedes det, at få flere patienter i træningsgruppen til at udøve hård fysisk træning og i længere tid end kontrolgruppen. Trods et

højere aktivitetsniveau fra baseline til 3 måneder, var det ikke muligt at identificere en signifikant forskel mellem grupperne målt på kondition, generel trivsel og på blodprøver. Fremtidige resultater vil vise om interventionen havde en langtidseffekt, eller om det kræver mere intensiv træning, at opnå effekt på hjerte-kar sundhed, nedsætte risikoen for nyt slagtilfælde og fremme kognitiv funktion hos denne patientgruppe.

Introduction

Stroke

Stroke is the fourth leading cause of death in the United States (US) and one of the leading causes of acquired disability worldwide (10). In the US around 800,000 people suffer from a stroke each year (11). According to the Danish National Patient Registry the annual incidence in Denmark is approximately 12,500 (12).

Stroke can be caused by an event of either a cerebral haemorrhage or by cerebral ischemia. Ischemia is the most frequent cause of stroke and is a results of a decrease in blood supply to brain tissues due to either thrombosis, embolism or decreased system perfusion (13). Cerebral thrombosis results in reduced blood flow caused by a local clot formation. A cerebral embolism is caused by a more distant clot formation, most commonly from the heart or carotid arteries, and transported by the bloodstream before occluding the cerebral arteries. Finally, decreased system perfusion is caused by low perfusion pressure mainly due to cardiac pump failure (13) (**Figure 1**). Reduced blood supply to an area of the brain leads to a lack of oxygen and glucose, resulting in the death of brain cells and either temporary or permanent tissue injury. The tissue injury may be visualised by either a computed tomography scan (CT) or a magnetic resonance imaging (MRI) scan of the brain (13).

Small-artery occlusion/lacunar stroke

Approximately one fourth of all ischemic strokes are identified as small-artery occlusion or lacunar stroke (14, 15). It is more frequent in patients with higher age, in men more than women, and in patients with a family history of stroke (16). A lacunar stroke is defined according to the Trial of Org. 10172 in Acute Stroke Treatment (TOAST-criteria) (17, 18) as a small-artery occlusion (a lacune) with often monosymptomatic clinical syndromes and verification of a corresponding small ischemic lesion on CT scan or MRI scan. The lesion is located in the white matter, basal ganglia, pons or brainstem with a diameter < 2 cm in the acute state. No cardiac source for embolism and no stenosis of the carotid arteries greater than 50% in the ipsilateral artery should be present. A history of diabetes mellitus or hypertension supports the clinical diagnosis (17). Previous study has shown that the TOAST-criteria has good inter-rater reliability in the acute stage of ischemic stroke, even when rated by two junior registrars (19).

Symptoms of lacunar stroke

Clinical symptoms reflect the often-small single lesion. Neurological deficits may occur suddenly, progressively, or in a fluctuating manner and can be present as sensory deficit, motor deficit, or language deficit (20). Because the lesion is small a fast recovery within weeks is often seen, leaving no or only minor deficits in the patients (20) (**Figure 1**). Lacunar stroke is most often a symptom of a more widespread and progressive cerebral small artery disease. Thus, lacunar strokes are associated with progressive cognitive decline and a two-fold increased risk of developing dementia (3). The highest prevalence of cognitive impairments was found within the first month after ischemic stroke (21) with mental speed and attention being the most impaired domains in both the acute phase (< 1 month) and after three months (21).

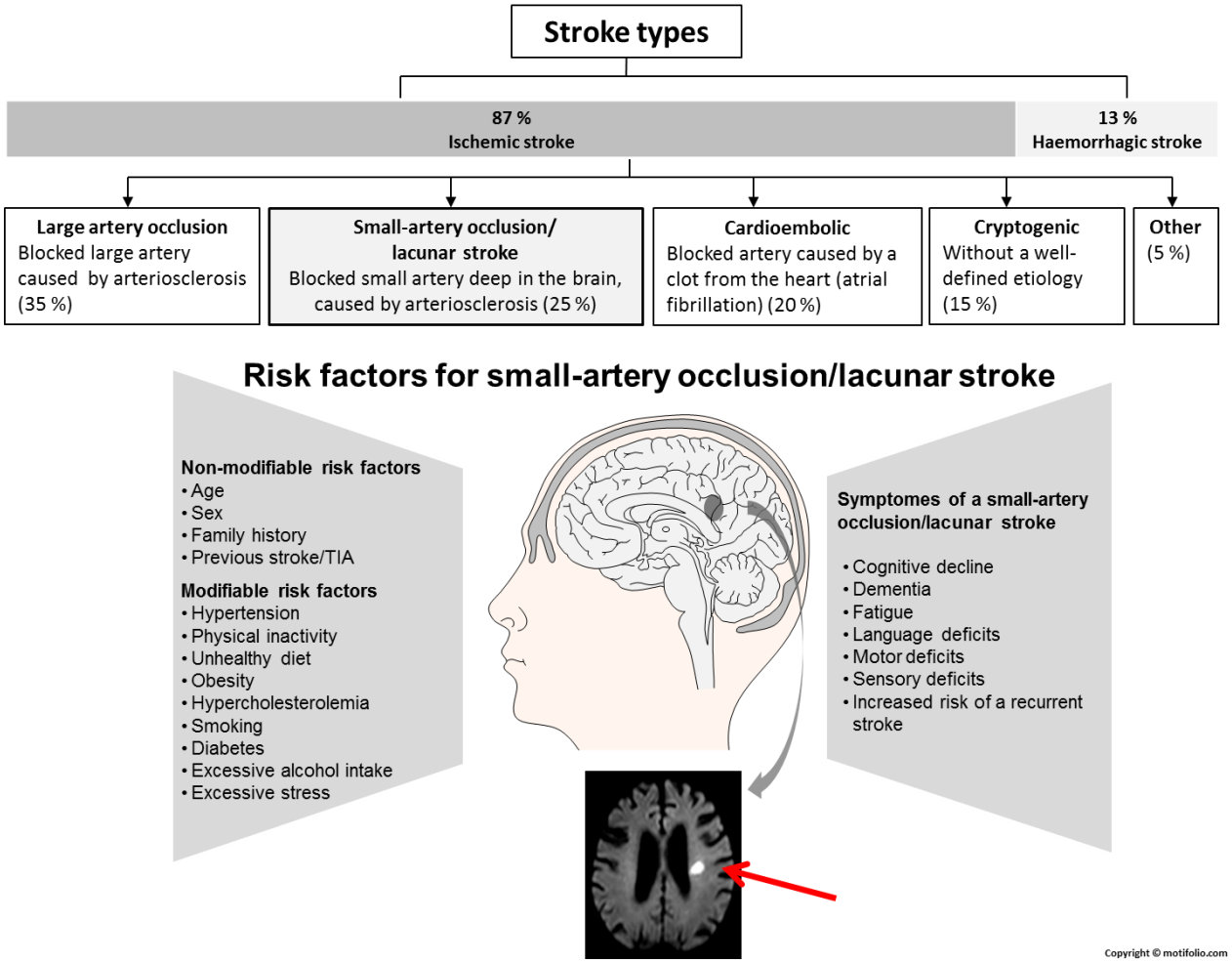

Figure 1. Subgroups of stroke patients with risk factors, and symptoms of a small-artery occlusion/lacunar stroke (15, 20, 22)

Risk of recurrent stroke

Patients with lacunar stroke have an increased risk of a recurrent stroke and other cardiovascular events (23), and within the first 90 days from stroke onset the prevalence is between 3.7–6.7% (24, 25). The annual risk of a recurrent ischemic stroke or transient ischemic attack (TIA) is approximately 3–4% (26). However, the number of incidence of recurrent stroke has decreased over the years (24, 27). This may be due to a hyper-acute evaluation by stroke specialists at the acute hospital ward and early introduction of secondary stroke prevention strategies, like medication (24). Stroke prevention is both important from a clinical perspective and from a general health perspective. From both perspectives, the aim of stroke management is to minimize deficit and prevent recurrence (28). A recurrent stroke is usually more debilitating, with worse prognosis and outcome, and with a higher rate of either rehospitalisation or discharge to long-term care facilities compared to patients with first-time stroke (28).

Risk factors for stroke

Risk factors of a recurrent stroke can be divided into three groups: 1) non-modifiable risk factors including age, sex, and family history (16), 2) medically modifiable risk factors e.g. hypertension, hypercholesterolemia and diabetes, and 3) behavioural modifiable risk factors such as diet, smoking, alcohol consumption and inactivity (29) (**Figure 1**).

The greatest risk factor for stroke is hypertension (30) and for patients with a recent lacunar stroke or TIA the blood pressure is recommended to be <130/90 mmHg (31). Hypertension can be targeted with antihypertensive medication and/or physical activity which both lowers the blood pressure (31, 32). Hypercholesterolemia is another modifiable risk factor reduceable with lifestyle modifications and/or statin therapy (31). The European guidelines on patients with cardiovascular disease recommend a total cholesterol level < 4 mmol/L, LDL < 1.8 mmol/L and HDL > 1 mmol/L (33). Also, early screening and identification of diabetes after a stroke or TIA is recommended in addition to an aggressive control of hyperglycaemia (fasting glucose < 5.6 mmol/L) (31).

Behavioural modifications are important to include in an everyday life. This was confirmed in a large American cohort study reporting risk of stroke in healthy individuals (34). A reduced risk of ischemic stroke was particularly attributed to a healthy lifestyle. The study defined a low-risk lifestyle by no smoking, BMI <25kg/m^2, moderate alcohol consumption, eating a healthy diet (lowering amount of sodium, eating fruit, vegetables and increasing fibre-rich foods), and regular

physical activity ≥ 150 minutes of weekly moderate-intensity activity, 75 minutes of vigorous-intensity activity, or an equivalent combination.

In a Swedish cohort with ten years follow-up (35) they explored the impact of healthy lifestyle in men at high risk of stroke (men without a stroke history but with a history of cardiovascular risk factors) and showed that healthy lifestyle patterns were associated with a reduced risk of stroke (35). Complying with all five behavioural lifestyle modifications (listed above), lowered the risk of stoke with 72% compared with men who only complied with 0-1 modification. Adapting to a healthy lifestyle is recommendable, however, the challenge is how to best make patients change their lifestyle after a stroke.

Risk awareness

The causes of stroke are multi-factorial (30) and so are the causes for non-compliance to the behavioural modifiable risk factors. Poor patient awareness and knowledge about cardiovascular risk factors have been reported as possible causes (36, 37). A study investigating the knowledge of risk factors in patients with stroke (38) showed that the patients had a low understanding of stroke etiology. Only 42% of the patients could identify risk factors for recurrent stroke. The study also illustrated that patients who recognized having a high risk of a future stroke were more likely to undertake lifestyle changes, compared with those who did not have the same insight (38).

Consequently, patient motivation is essential and education about risk awareness is highly important. The challenge is how the information is understood and implemented by the patient and relatives (39).

The effect of physical exercise post-stroke

There is increasing evidence on the beneficial effect of physical exercise on motor function and mobility post-stroke especially when compared with usual care (40). As shown in a Cochrane review there is an ongoing and controversial debate on which is the most effective therapeutic approach in stroke rehabilitation (40). The optimal and recommended dose (length of programme, frequency, duration, and intensity of sessions) of physical exercise is yet unresolved (40). However, aerobic exercise reduces disability after stroke allowing patients to do activities of daily living, and on long-term basis it potentially reduces the risk of cardiovascular events (4). Thus it is recommended to be implemented into post-stroke rehabilitation programmes (4). Furthermore, there is room for improvement in exercise capacity, as the aerobic capacity among patients with

stroke is reported to be as low as 50% of the sex matched and age matched level, in sedentary individuals (41, 42). This low level of cardiorespiratory fitness is also seen in patients with a TIA or minor stroke (including lacunar stroke) (43). In this recent RCT study, the reduced level of cardiorespiratory fitness is not explained by the stroke-related factors (such as stroke characteristic and a history of stroke) but apart from sex and age, by a history of vascular disease, pulmonary disease and vascular risk factors (e.g. obesity, hypertension and inactivity) (43).

High methodological studies investigating efficacy of exercise on mortality and morbidity (including recurrent stroke) following lacunar stroke are lacking (44). Instead most exercise studies aim to reduce risk factors of cardiovascular events (45). Often do the patients have multiple risk factors, and the studies use multifactorial non-pharmacological approaches including physical exercise, making it challenging to identify the most effective strategy (29).

Two recently published reviews, investigated the efficacy of physical exercise combined with other interventions following stroke and TIA. They suggested independently that interventions including aerobic exercise are effective in reducing systolic blood pressure (29, 46), reducing fasting insulin and fasting glucose and increasing high-density lipoprotein cholesterol level (46). However, it seems crucial to include physical exercise in the intervention when aiming to reduce risk factors of stroke. A recent Cochrane review, only using educational and behavioural interventions did not show an effect on adherence to recommendations for secondary stroke prevention (47). The studies targeted an improvement of blood pressure, BMI, lipid profile, blood glucose (HbA1c), medication adherence to reduce the incidence of recurrent cardiovascular event. In general the available literature is scarce and inconsistent concerning the effect of high-intensity interval training versus moderate-intensity continuous training in the prevention of cardiovascular risk factors (48) which warrants further studies on the subject.

Barriers and motivators to physical exercise after stroke

How can we motivate individuals after stroke to be physically active and what is potentially preventing them from being physically active? A multicentre study in stroke survivors did not find any effect of repeated encouragements and verbal instructions on physical activity after ischemic stroke (49). More action and less talk are needed and having an intention to change behaviour is not necessary associated with an actual change. Two reviews have investigated barriers and motivators for participation in physical activity in patients with neuromusculoskeletal conditions

including stroke (50) and in patients with stroke (51). They highlight environmental barriers and personal barriers as the most common barriers for not engaging in physical activity after stroke. Environmental barriers included accessibility to buildings and training facilities, lack of transportation, and economic cost of the training services (52-55). While the personal barriers included health problems and stroke-related impairments, lack of motivation, fear of recurrent stroke, and lack of knowledge about how and where to exercise (52-55). The strongest motivator for physical activity was social support from friends and family and the possibility of meeting others with stroke which could provide social support for participation (having an exercise partner) (53, 54, 56). Furthermore, post-stroke fatigue is an additional barrier and a common disabling symptom (57) reported by more than 50% of stroke survivors (58), even in patients with minor stroke or TIA (59). Fatigue reduces participation in everyday life and in physical activity (60). However, knowing that post-stroke fatigue is a barrier to physical activity, it may be promising for the time-efficient exercise modality, high-intensity interval training (HIIT).

High-intensity interval training

HIIT is characterized by aerobic exercise performed in intervals of high intensity interspersed with periods of rest or lower-intensity exercise (48). HIIT varies in frequency, duration of exercise sessions, number and duration of intervals, exercise intensity, and in duration and mode of recovery (active/passive) (61). The definition of heart rate intensity is different across studies (48) and it varies between 75-95% of maximum heart rate (HR) corresponding to ≥15 in rating of perceived exertion (RPE) (62-64).

Evidence suggests that HIIT has the potential of inducing changes in physiological and health related markers similar to or even better than moderate-intensity continuous training (MICE) in individuals with heart diseases (61, 65). Investigating the effect of HIIT in patients with cardiovascular diseases showed an improvement in aerobic capacity (cardiorespiratory fitness (VO_{2max}), endothelial function, and quality of life (62, 66).

HIIT requires a lower time commitment and a reduced total exercise volume compared with MICE (67). This is important from a clinical and public health perspective in the prevention of chronic diseases, as "lack of time" is a commonly used excuse for not participating in regular physical exercise (68-70). Another interesting aspect of HIIT is that it seems more enjoyable compared with MICE as reported by the patients, which is an important factor for exercise adherence (71). In a study comparing HIIT to MICE, the participants insinuated that the variation in the activity profile

during HIIT caused the greater post-exercise feeling compared with the "boring" steady-state continuous approach (71). However, the study could not conclude whether the positive attitude towards HIIT was due to the variation in the activity profile or due to periods of increased exercise intensity or a combination (71). Of note, the exercise modality varies across the studies and the most commonly used modalities for patients with cardiovascular diseases are treadmill training and ergometer cycling (48). With a number of varying HIIT protocols used in the literature we may conclude that so far no ideal HIIT-protocol is agreed upon in the treatment and prevention of cardiovascular disease (48).

High-intensity interval training and safety

An important issue with application of HIIT in stroke patients is the safety. Studies have shown that HIIT is safe and well tolerated in patients with cardiovascular diseases and no adverse cardiac events or other life-threatening events have been registered during intervention (62, 66, 72). This was confirmed in a recent study investigating the safety during HIIT on treadmill in patients with chronic stroke (73). They found no significant arrhythmias or myocardial ischemia, no orthopaedic injuries (e.g. fall, pain or ankle sprain), one patient (out of 18) experienced a hypotensive response but continued the exercise. To reduce the risk of adverse events during HIIT exercise post-stroke, precautions should be taken and address the recommendations from national guidelines (74). Such recommendations include exercise testing with ECG monitoring prior to exercise, due to the high rate of silent myocardial ischemia (20–40%) within the stroke population (75). Monitoring blood pressure prior to exercise is recommended and a hypertensive response cut-off of 250/115 mmHg is recommended for termination of testing (76). Likewise, blood pressure control also helps to avoid a hypotensive response (e.g. going from a high burst of exercise to a recovery period without exercise), which favours an active recovery period. On the other hand, an active recovery may reduce the HIIT tolerance as many patients struggle with post-stroke fatigue (57). Also, adequate hydration is important when performing aerobic exercise to reduce risk of dehydration and confusion. Several studies using treadmill exercise as training modality in HIIT in patients with stroke also describes that they practice safety precautions by using a harness and bar handles. So far, all the HIIT intervention in stoke populations have been supervised by a physiotherapist (73, 77-82). Thus, evidence suggest that HIIT is a safe approach, more and preferably larger studies investigating safety issues in stroke populations are requested.

High-intensity interval training in stroke

A literature search in MEDLINE (April 2018) did not result in studies reporting effect of HIIT in patients with lacunar stroke. By expanding the search to include patients with stroke in general, a small number of studies were found (n=10). A recent published review updating the literature on HIIT in stroke rehabilitation, confirmed the existing literature (72). Five training studies (77, 81-84) (3 RCTs (81-83), one pilot study (84) and one feasibility study (77)) have investigated different aspects of HIIT in patients with stroke. The remaining 5 papers reported single-session studies (2 studies with outcome measures of neuroplasticity (78, 85), 2 studies with outcome of exercise tolerance (73, 80) and one study evaluated exercise modality (treadmill versus recumbent stepper) (only available as abstract).

All three RCTs investigated short-term effect (maximum 4 weeks) of HIIT versus MICE (81-83) performed as individual sessions on a treadmill with gait as the outcome measure (**Table 1A-1C**). One study investigated feasibility whereas two investigated effect of different gait speed. All participants were ambulatory patients with stroke, recruited from <1 month after stroke onset to >6 months post stroke. The studies used different HIIT protocols, they all applied safety precautions and used a fall protective harness, and every session was supervised by a physiotherapist. All three studies found that HIIT was superior to MICE in terms of walking speed. The fact that only three RCTs have investigated effect of HIIT in patients with stroke, reveals an urgent need for more high-quality studies including a larger number of patients, preferably multicentre trials across countries within this field of research.

Author, year, country	Aim	Participants	Age, years mean ±SD	Intervention, modality	Number of participants in analysis Randomisation	Safety precautions
Boyne P. et al (2016) (83), USA	Assess the feasibility and justification for a RCT comparing HIIT and MICE	Ambulatory chronic stroke patients (> 6 month)	HIIT: 59±9 MICE: 57±12	HIIT vs. MICE Treadmill training	Total (n=16) HIIT (n=11) MICE (n=5) Randomisation ratio: 2:1 of HIIT	• Stress test on the treadmill with ECG-monitoring (prior to exercise) • Fall protection harness • Elastic band safety limit • Handholds • A physical therapist present during exercise + research assistant present for data collection
Lau KWK. et al (2011) (82), China	Compare the effect of speed-dependent (sprint training) treadmill training to speed-stable treadmill training	Ambulatory patients with stroke in sub-acute phase (< 1 month from stroke onset)	HIIT: 70±11 MICE: 72±9	HIIT vs. MICE (Speed-dependent vs. steady-speed) Treadmill training	Total (n=26) HIIT (n=13) MICE (n=13) Randomisation ratio: 1:1	• Fall protection harness • Handholds • A physical therapist present during exercise
Pohl M. et al (2002) (81), Germany	Compare the effect of speed-dependent treadmill training to 1) treadmill training with slow-increase of velocity and 2) to conventional gait training (a three-armed study)	Ambulatory patients with stroke (> 4 weeks from stroke onset)	HIIT: 58±11 MICE: 57±14 Control:62±11	HIIT (speed-dependent) vs. MICE (limited progressive) vs. Control (conventional) Treadmill training	Total (n=60) HIIT (n=20) MICE (n=20) Control (n=20) Randomisation ratio: 1:1:1	• Stress test on the treadmill with ECG-monitoring (prior to exercise) • Fall protection harness with bodyweight support (max 10 % of the patient´s weight) in session 1-3 • Safety belt • A physical therapist present during exercise + supervision from a nurse who controlled blood pressure

Table 1A, 1B and 1C. Published randomised controlled trials investigating HIIT in patients with stroke (Revised from (72))
Table 1A. Demographics

Author, year, country	Frequency, duration and time	HIIT intensity	MICE intensity
Boyne P. et al (2016), USA	3 times/week, for 4 weeks (12 sessions) Each session: 25 minutes (incl. 3 minutes of warm-up, 2 minutes of cool-down)	Starting at 0.1 mph below max. safe speed and held for 30 seconds at max safe speed. Session 1-3: Bursts of 30 seconds, recovery of 60 seconds. Total HIIT time: 8 minutes Session 4-12, first 3 bursts: Bursts of 30 seconds, recovery of 60 seconds Session 4-12, burst 4+: bursts of 30 seconds, recovery of 30 seconds. Total HIIT time: 12.5 minutes	Speed maintained at 45 ± 5% HRR (session 1-6) Speed progressed to 50 ± 5% HRR (session 7-12)
Lau KWK. et al (2011), China	5 days/week, for 2 weeks (10 sessions) Each session: 30 minutes	Initial gait speed was determined by the fastest over-ground gait speed (assessed by 10-meter walking test before each session) Burst: Maximum safe speed for 30 second Recovery: 2 minutes of rest (no activity) Progression: if a trial was successfully completed → speed increased by 10% on the next trial. If a trial failed on completion → speed reduced by 10% on the next trial Total HIIT time: 4 minutes for each trial (3-4 trials)	Fastest over-ground gait speed for 30 minutes (assessed by 10-m walking test before each session)
Pohl M. et al (2002), Germany	3 times/week, for 4 weeks (12 sessions) Each session: 30 minutes	5 minutes of warm-up at 50% of max gait speed Burst: during a period of 1-2 minutes the gait speed was increased to max. safe gait speed and then held for 10 sec. Recovery: active recovery – until heart rate returned to resting level. Progression: if a trial was successfully completed → speed increased by 10% on the next trial. If a trial failed on completion → speed reduced by 10% on the next trial Total HIIT time: 4 minutes for each session (3-4 trials)	Gait speed increased < 5% of max initial walking speed each week (20% over 4 weeks) Control: 45 minutes of gait therapy by proprioceptive neuromuscular facilitation and Bobath concepts

Table 1B. Intervention overview
HRR: Heart rate reserve

Author, year, country	Primary endpoint	Secondary outcomes	Assessment, time points	Results, Significant findings	Attendance	Adverse events
Boyne P. et al (2016), USA	Aerobic capacity (VO_{2peak} and ventilatory threshold) (mL/kg/min)	• Metabolic cost of gait • Fractional utilization (%) • Fastest treadmill speed (m/s) • 10-meter walking test (m/s) • Six-minute walking test (m)	4 weeks	• Ventilatory threshold, effect size: 1.95 compared to MICE • Fractional utilization of O_2, effect size: 1.74 compared to MICE • Fastest treadmill speed, effect size: 1.68 compared to MICE • 10-meter walking test, effect size: 1.44 compared to MICE	85% for HIIT sessions	None
Lau KWK. et al (2011), China	10-meter walking test (min/sec) Berg´s Balance Scale	Walking speed, cadence and stride length was calculated from the 10-meter walk test.	2 weeks	• Increased gait speed in HIIT compered to MICE • Increased stride length in HIIT compared to MICE Increase in Berg´s Balance Scale in the control group.	100%, All participants completed 10 sessions	None
Pohl M. et al (2002), Germany	Functional Ambulation Category	• Walking speed (min/sec) • Cadence (steps/min) • Stride length (meter)	2 and 4 weeks	• Walking speed: HIIT was superior to MICE $p<0.001$, HIIT was superior to control: $p<0.001$ • Cadence: HIIT was superior to MICE $p< 0.007$, HIIT was superior to control: $p<0.001$ • Stride length: HIIT was superior to MICE $p<0.001$, HIIT superior to control: $p<0.001$ • Functional Ambulation Category: HIIT was superior to MICE $p<0.007$, HIIT was superior to control: $p<0.001$	100%, all participants completed 12 sessions	None

Table 1C. Main reported outcomes

Measurement of cardiorespiratory fitness in patients with stroke

The gold standard for measuring cardiorespiratory fitness is the direct measure of maximal oxygen uptake, VO_{2max}. Aerobic capacity is defined as the maximum amount of oxygen the body can use during intense exercise (86). The measurement involves a graded exercise test on either a treadmill or a stationary bicycle in which the exercise intensity is increased until maximum effort, while measuring ventilation and concentration of oxygen and carbon dioxide. The VO_{2max} is expressed as millilitres of oxygen per kilogram of body mass per minute (ml/kg*min). The assessment of VO_{2max} in patients following stroke may be challenged by stroke-specific impairments (e.g. muscle weakness, reduced balance, and fatigue) or by the requirement of advanced and expensive equipment, not generally available in all rehabilitation settings.

Despite these challenges, assessment of VO_{2max} may be feasible to perform following stroke. This was shown in a recent systematic review exploring several protocols for measurement of VO_{2max} in patients with stroke (87). In the review, three studies of nine assessed VO_{2max} 10-26 days post-stroke, in small samples (6-20 patients included) using different exercise modalities (treadmill, stationary bicycle and semi-recumbent bicycle) and varying protocols (88-90).

In case a direct measurement of VO_{2max} is not feasible, an estimation of VO_{2max} using either a maximal or sub-maximal exercise test can be done. A maximal exercise test can be performed on e.g. a stationary bicycle measuring the resistance/power output in Watts (91). The patient exercises with progressively increased intensity, until maximum effort. When the level of maximal effort is reached, the VO_{2max} is estimated from the power output registered in Watts and the number of seconds exercising at maximum level (91). This test does not require advanced and expensive equipment, but it still requires the patient to exercise at a maximum level, which may be a challenge in patients with stroke-specific impairments.

A sub maximal exercise test is another way of estimating $VO_{2max,}$ from simple heart rate measures. The Astrand-Ryhming cycle ergometer test is a sub maximal exercise test (single-stage) to estimate VO_{2max}, based on age, sex, resistance/power output in Watts and heart rate (92). The patient exercises on a stationary bicycle for six minutes with a cadence of 60 rounds per minute (rpm) and an estimated work rate (power output) based on sex and individual fitness status is applied. The purpose is to reach a steady state heart rate between 130-170 beats per minute during

the last minute of exercise. An average heart rate value from the last 15 seconds of exercise is calculated to estimate VO_{2max} from a nomogram based on estimated maximum heart rate (92).

This test does not require expensive equipment, but it depends on an estimation of both work rate /power output and heart rate. The heart rate will be inaccurate if the patient is on beta blockers, which could be the case, as nearly 62% of patients with stroke may have a silent coronary artery disease and are prescribed beta blockers (93). In patients on beta blockers, the maximum heart rate may be decreased as much as 30% (94), why the equation for estimating maximum heart rate should be adjusted accordingly.

Another sub maximal exercise test is the Graded Cycling Test with Talk Test which is not based on heart rate. This test does not estimate VO_{2max} but provides a measure of perceived effort.

When using the Talk test (TT) for exercise testing, the individual performs progressively more intense exercise (e.g. walking, running, or cycling) while reciting a standard text passage either from memory or from a cue card. Following the recitation, the individual is asked: "are you able to speak comfortably?". There are three possible answers: "yes", "unsure" and "no". The individual can answer "yes" and "unsure" as many times as he/she wants and when the answer is "no" the test terminates. Previous studies showed that the positive stage in the TT (e.g. "yes, I can speak comfortably") is below ventilatory threshold (9, 95). When the relative exercise intensity approached the ventilatory threshold the ability to speak is usually rated as equivocal (e.g. "Yes, I can speak, but not entirely comfortable", corresponding to the answer "unsure"), and when the exercise intensity exceeded the ventilatory threshold the speech ability is rated "Definitely not comfortable" , corresponding to the answer "no" (95). The positive correlation between the TT and ventilatory threshold was observed in both elite and recreational athletes (96, 97), in sedentary and healthy adults (97-99), and in cardiac patients (100-103). Furthermore, the literature show that the TT is useful to guide exercise intensity in individuals who need guidance (e.g. sedentary individuals and individuals with chronic diseases) simply by instructing them to adjust their exercise intensity to the highest level, matching comfortable speech (9, 104).

The length of the standardised text passage is also of importance. A shorter text passage (~31 words) is shown to be more user friendly (more convenient and easier to memorize) versus a long text passage (90-100 words). Previous studies have shown when using the short text, the ventilatory threshold occurs close to the last positive stage of the TT (9, 105).

The TT has been used with many different incremental exercise protocols e.g. during treadmill walking (98, 100, 101), during corridor walking (100), and on a stationary bicycle (96, 102, 106).

When the TT is used with the Graded Cycling Test protocol (GCT), it is performed on a stationary bicycle (107). It uses a ramp-protocol with a 15 Watt (W) increase in exercise intensity each minute and the power output are registered in Watts (**Figure 2**).

The GCT-TT has high reliability and minor measurement error in patients with ischemic heart disease (107). Furthermore, the GCT-TT was responsive to changes after eight weeks of cardiac rehabilitation (108), but so far no studies have investigated the validity of the GCT-TT against maximal oxygen consumption in any patient groups.

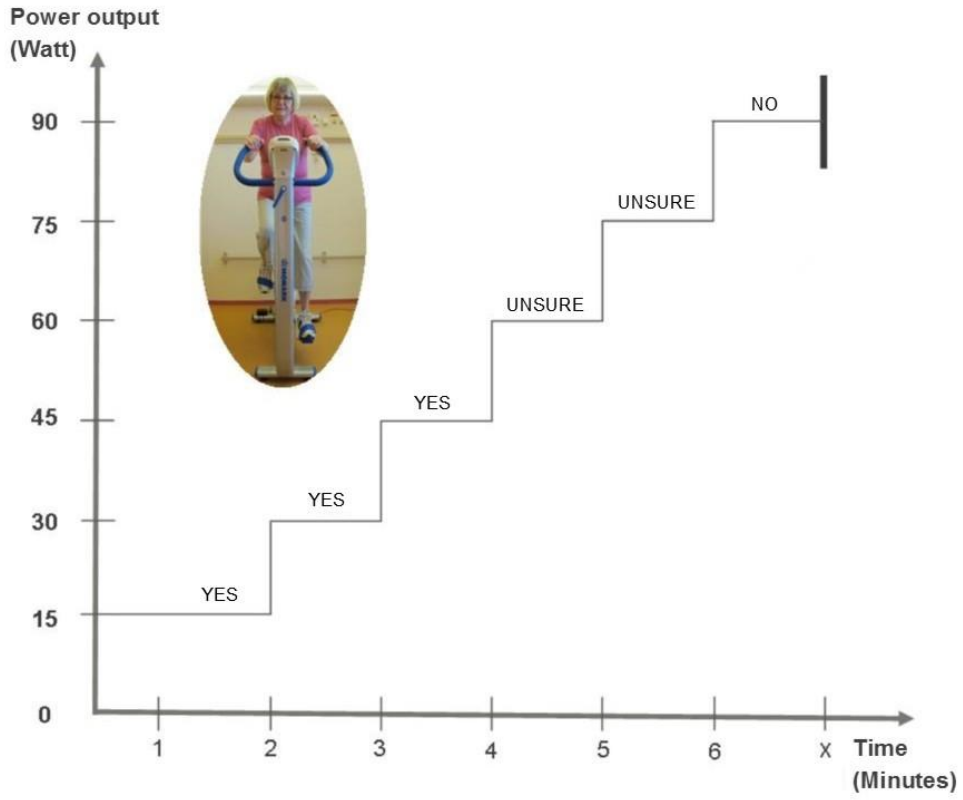

Figure 2. Exercise protocol for "The Graded Cycling Test with Talk Test"
The workload on the stationary bicycle increases with 15 Watts every minute. At the end of each minute the patient recites a standardised text passage, followed by the question: "are you able to speak comfortably?". If the patients answers "yes" or "unsure" the test continues. When the answer is "no" the test terminates and the power output in watt is registered.

The most frequently used modality for exercise testing in Europa is the stationary bicycle. This is in contrast to the Unites States where the use of treadmill exercise is more prominent (76). It is an advantage to use the bicycle as an exercise modality, as many Danes are familiar with cycling on leisure basis or as a frequent way to commute. Also, cycling is an exercise modality which is

realistic and possible for our patient population, even if they have balance issues, or a light hemiparesis. Anecdotally, it is more common to use submaximal exercise test in Scandinavia compared to the United States where maximal exercise test is used.

The GCT-TT is a submaximal exercise test measuring perceived effort, and it is easy to use in clinical practice. It is time effective and it does not require expensive equipment (only a stationary bicycle), which makes it applicable in many clinical rehabilitation settings (in both hospital settings and in community settings). Another advantage, is that the test is assessor-independent as it is the patient who identifies the intensity level at which he/she cannot speak comfortably. Also, the GCT-TT is reliable and has minor measurement error in patients with ischemic heart disease (107). The GCT-protocol is a well-known test and frequently used in clinical practice in Denmark. Additionally, the literature shows that the TT is usable to prescribe exercise intensity (9, 104), which also makes it an attractive choice in our study. Thus, we wanted to investigate if GCT-TT is feasible and reliable in patients with lacunar stroke with the purpose to use it as a guide for exercise intensity, and to estimate cardiorespiratory fitness in our randomised controlled trial.

Effect of exercise on metabolism and cardiovascular function

Blood pressure

Hypertension is the greatest risk factor for first-time stroke (30, 109) and for recurrent stroke (31, 32). A recent systematic review showed a reduction in both systolic blood pressure and diastolic blood pressure after exercise, compared with usual care in patients with stroke or TIA (110). Furthermore, exercise interventions initiated within 6 months post-stroke or TIA were more effective than exercise interventions initiated after 6 months (110).

BMI

Obesity is defined as a BMI≥30 kg/m^2 and is associated with increased risk of cardiovascular disease and first-time stroke (31). Despite this association, it has never fully been established whether obesity is a risk factor for recurrent stroke (31). Research indicated that obese patients with stroke had a minor risk compared with lean patients with stroke (111), which was referred to as the obesity paradox. A large RCT multicentre study (look AHEAD study) (112) investigated the effect of a behavioural intervention, including unsupervised exercise for weight loss on cardiovascular event in patients with type 2 diabetes, and did not find a reduced risk. Similarly,

two recent systematic reviews showed no significant effect of exercise on BMI compared with usual care in patients with stroke or TIA (46, 110).

Diabetes/fasting insulin level

Diabetes is associated with an 60% increased risk of recurrent ischemic stroke (113, 114). The effect of exercise on cardiovascular risk factors following stroke, was observed in a recent systematic review, with a beneficial exercise effect on reducing fasting insulin level (46). However, this effect was only based on three studies included in the meta-analysis and thus potentially represented an overestimation of effect. This is a potential area for future research.

Endothelial function

Reduced endothelial function is associated with increased risk of stroke (115, 116), cardiovascular disease (117), hypertension (118) and hypercholesterolemia (118). It is characterized by a reduction of the vasodilators response (nitric oxide (NO)) and/or an increase in endothelium-derived contracting factors and precedes the development of arteriosclerosis (119, 120). A study investigating the relationship of endothelial function and stroke subtypes found that endothelial function varied with stroke types; best endothelial function in patients with cardioembolic stroke, and worst in lacunar and large artery stroke (121). The protective effect of exercise on endothelial function has been shown in patients with cardiovascular disease, regardless of etiology (66). This protective effect may be extended to include patients with cerebrovascular disease, as these groups of patients share the same pathophysiological mechanisms (122, 123). However, the effect of HIIT on endothelial function has only been shown in studies including patients with cardiovascular disease, but not yet in patients with cerebrovascular disease (66) (**Figure 3**).

Effect of exercise on post-stroke complications and deficits

Mental well-being

Patients with symptoms of a mild stroke with minor disabilities are assumed to achieve full recovery, thus quality of life may not be affected. However, a decline in life satisfaction was detected six month after stroke in patients with mild symptoms of a stroke (124). The cause of such decline in quality of life was; a decreased ability to uphold usual employment, reduced social activity, problems with concentration, decreased driving ability, and irritable mood (124). Overall,

a Cochrane review concluded that few studies are available and with inconsistent results to detect an effect of physical exercise on quality of life measures in patients with stroke (4).

Cognitive function

Following a lacunar stroke, the patients are at high risk of developing cognitive decline and dementia (3). Little is known on the effectiveness of physical exercise on cognitive function after stroke (4). There may be a trend towards exercise having a positive effect on cognitive function in patients with stroke, but more studies are warranted (4).

Post-stroke fatigue

Fatigue is a common symptom immediately after stroke (57) and it tends to persist for months or years in a high number of patients (125). It is distressing with long-term problems and contributes to decreased quality of life and increased risk of depression (125, 126). There is yet little information on the effectiveness of exercise on post-stoke fatigue (127). A Cochrane review showed no effect, of non-pharmacological intervention (education program and mindfulness program), on post-stroke fatigue, and in general insufficient evidence on the efficacy of any intervention to prevent or treat post-stroke fatigue (125). However, a Cochrane review evaluating aerobic exercise in patients with chronic fatigue syndrome, showed that exercising is safe, and the patients may benefit and feel less fatigued after exercise (128).

Depression

Post-stroke depression is common and the risk is especially high in the first months after stroke (129). The mechanisms of post-stroke depression are poorly understood, but the literature support that patients should be screened routinely, to address symptoms early (130). Few studies with various methodological quality are available to measure effect of exercise on mood post-stroke (4). Different outcome measures of depression are applied with various types of exercise (measured as secondary outcomes), why no consistent results can be drawn (4). However, a systematic review including both resistance training and aerobic exercise indicated a beneficial effect of physical activity on reducing depressive symptoms in patients post-stroke (131). The small effect was detected in both the sub-acute stage (<6 months) and in the chronic stage (≥6 months), but the effect was not maintained after exercise termination.

Chronic stress

Chronic stress is associated with increased risk of cardiovascular disease (132), on par with other cardiovascular risk factors such as smoking, physical inactivity, heavy alcohol consumption etc., and it has previously been linked to the lifestyle habit that people have when feeling stressed (133). Recent research has explained how stress may be linked to cardiovascular disease (133). Chronic stress is associated with high activity in amygdala signalling to the bone-marrow to produce extra white blood cells which leads to arterial inflammation, potentially causing a cardiovascular event (133). There is a lack of knowledge on efficacy of exercise on stress impact in patients with stroke. A recent animal study has shown that exercise may improve stress associated symptoms and lower the risk of cerebrovascular dysfunction in rats (134). However, this may seem promising, but the clinical use is still questionable (**Figure 3**).

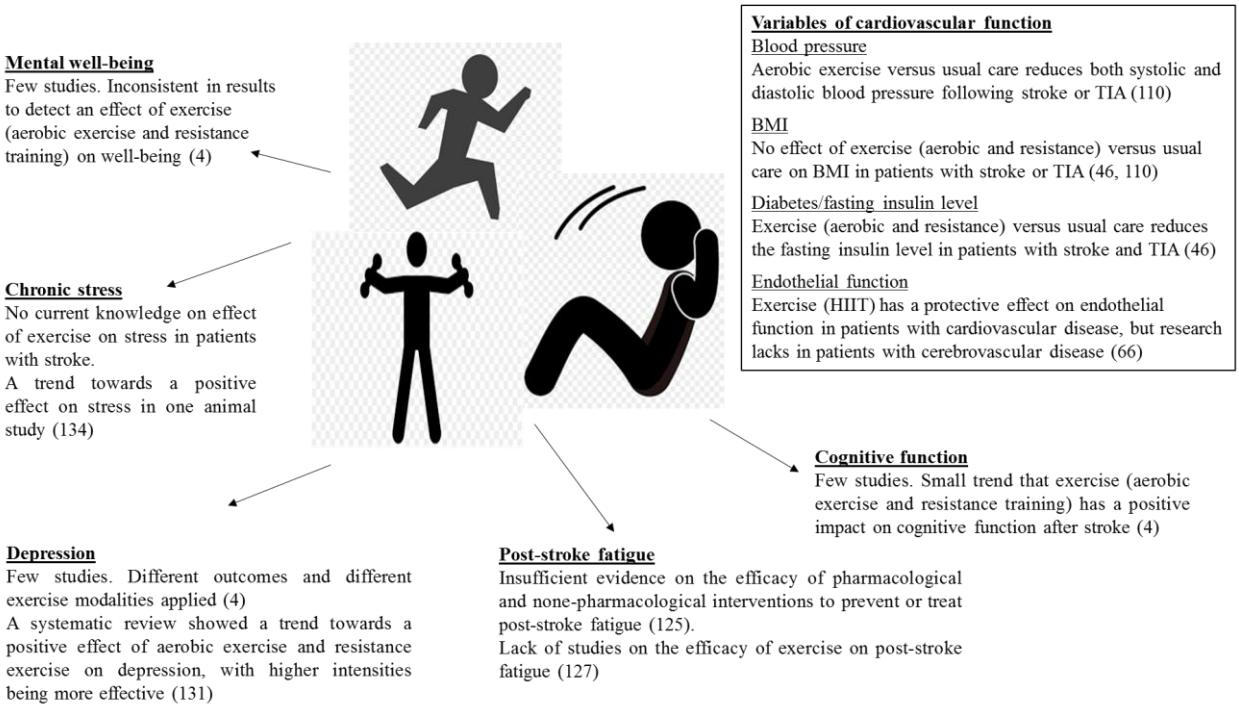

Figure 3. Post stroke complications and deficits and their response to exercise

Hypotheses and aims

In this thesis, we hypothesized that:

1. The Graded Cycling Test with Talk Test is a feasible and reliable outcome measure in patients with lacunar stroke.
2. Patients with lacunar stroke have a low level of physical activity, pre-stroke.
3. The level of pre-stroke physical activity is associated with post-stroke risk factors in patients with lacunar stroke.
4. Home-based high-intensity interval training is feasible and safe in patients with lacunar stroke.
5. Home-based high-intensity interval training may improve cardiorespiratory fitness and/or associated risk factors for stroke in patients with lacunar stroke.

Accordingly, the specific aims were to:

1. Conduct a methodological study investigating feasibility and test-retest reliability of the Graded Cycling Test with Talk Test.
2. Conduct a cross-sectional study evaluating pre-stroke self-reported physical activity in patients with lacunar stroke.
3. To evaluate associations between pre-stroke physical activity level and risk factors for stroke in patients with lacunar stroke.
4. Conduct a randomised controlled trial to investigate feasibility and safety of 12-weeks of home-based high-intensity interval training.
5. Compare changes in cardiorespiratory fitness and secondary outcomes (endothelial function, post-stroke fatigue, depression, cognition, mental well-being, physical activity, BMI, and lipids) among patients with lacunar stroke who are offered 12-weeks of additional home-based high-intensity interval training and those who are offered usual care only.

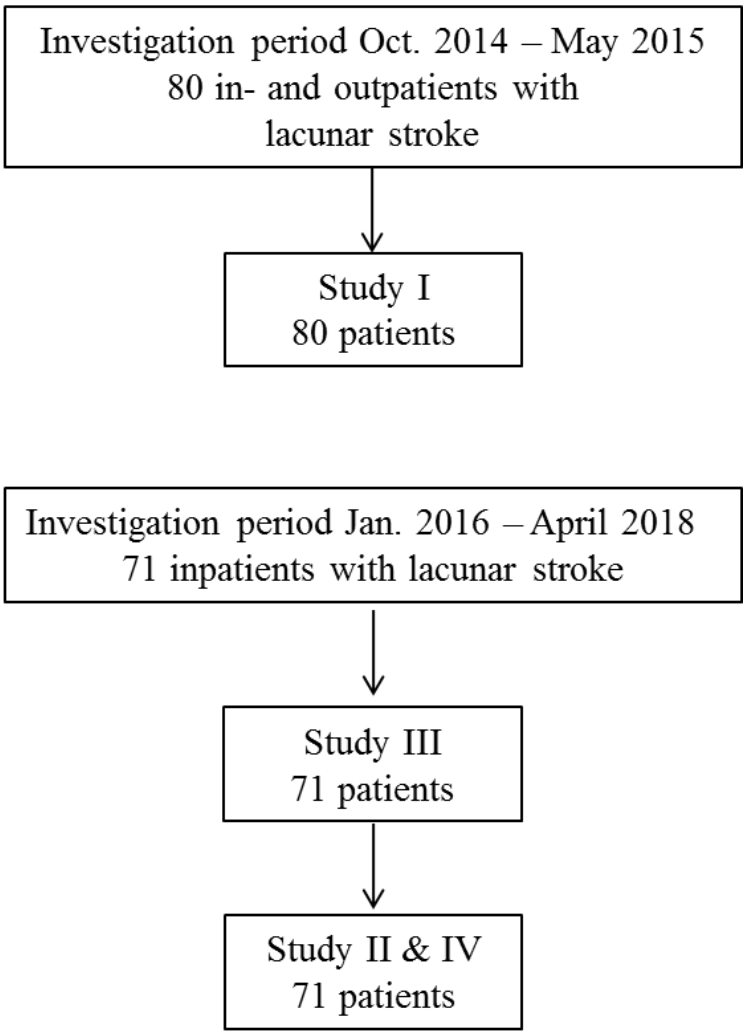

Figure 4. Overview of the investigation period, studies and patients in the thesis.
A detailed description of patient characteristic is provided in each study

Methods

This thesis is based on one protocol-study and three clinical studies and in the following section methodological considerations regarding aspects of all four studies are described. An overview of the studies and patients in the thesis is illustrated in **Figure 4**.

Methodological considerations

To enhance the quality and transparency of our studies, we have in the reporting of each study adhered to the guideline from the Equator network. In the reporting of the reliability study (study I) we adhered to the "Guideline for reporting reliability and agreement studies" (GRRAS) (135). In the protocol-study (study II) we followed the SPIRIT 2013 statement (136), in the reporting of the cross-sectional study (study III) we adhered to the STROBE guideline (137), and in study IV we have adhered to the guideline for randomised trials (the CONSORT 2010 statement) (138). Furthermore, for an optimal reporting of the therapeutic exercise intervention in the RCT, we have adhered to CERT-guideline (Consensus on Exercise Reporting Template) (139)

Study design

Three different designs were chosen because the objectives differed.

- A methodological study to test feasibility and reliability of the GCT-TT (study I).
  - To use GCT-TT as the primary outcome in the RCT, the outcome measure must be applicable in clinical practice and be able to measure with consistency in our target group.
  - The stability of the response in GCT-TT is dependent on the time interval between the two tests. The purpose is to avoid fatigue and natural remission of stroke symptoms to affect the response. Thus, we choose to perform the tests with one hour of rest in between.
  - The GCT-TT is independent of the tester. When using the GCT-TT the patients identifies the level where they were not able to speak comfortably any longer. Furthermore, this level is used to guide exercise intensity in the RCT (study IV).
- A cross-sectional study to explore self-reported pre-stroke physical activity in patients with lacunar stroke evaluating adherence to the international minimum recommendations on physical activity. Further to resolve associations between pre-stroke physical activity and risk factor for stroke (study III).

- An RCT with parallel-group design evaluating the effect of 12 weeks of additional high-intensity interval training at home in patents with lacunar stroke, versus usual care only (study II (protocol trial) and study IV (RCT)).

Patient selection

The following inclusion criteria and exclusion criteria were used in the patient selection in all four studies, except for including both in and out-patients in study I:

Inclusion criteria

- Patients with either first-time lacunar stroke or recurrent lacunar stroke. The diagnosis was verified by clinical examination by a neurologist and with recognition of stroke symptoms on CT scan or MRI scan. Lacunar stroke was defined as a small infarct (<2 cm in diameter, acute stage) according to the TOAST-criteria (17).
- Patients were enrolled consecutively within 21 days of stroke onset
  - We wanted the intervention to be initiated early after stroke, in the sub-acute stage
  - First, we had an inclusion period from 0-7 days, but it was challenging to enrol the patients in this limited time-frame. This, due to the time usage of routine examinations for stroke diagnosis and risk factors. Therefore, we made an amendment and extended the inclusion period to 0-21 days post-stroke (study IV).
- ≥ 18 years of age and able to give informed consent
  - By Danish law, individuals are legally independent from the year they turn 18.
  - According to ethical principles for individuals to involve in medical research, participation must be voluntary, thus informed consent must be signed upon enrolment (140).
- Able to speak, read, and understand Danish.
  - To perform the GCT-TT and to understand the purpose of the study the patients must be able to speak, read, and understand Danish.
- In the reliability study, we included both in- and outpatients with lacunar stroke as the purpose was to investigate whether the GCT-TT was applicable as an outcome measure in a broader range of patients with lacunar stroke varying in physical ability.

Exclusion criteria

- Patients with previous large artery stroke with sequelae preventing aerobic exercise on a stationary bicycle
- Atrial fibrillation
  - We investigated only patients with lacunar stroke and not patients with a cardioembolic cause as we wanted a homogeneous data set.
  - To prevent the risk of cardiac events during the trial
  - Atrial fibrillation was an exclusion criterion for the assessment of endothelial function using the EndoPAT2000 devise.
- Carotid artery stenosis
  - We wanted a homogeneous data set.
  - To prevent the risk of cardiac events during the trial.
- Uncontrolled hypertension
  - Patients not responding adequately to antihypertensive medication when applying treatment according to guidelines (31). The information is retrieved from the patient chart when including the patients.
- Symptoms or comorbidities that could prevent aerobic exercise on a stationary bicycle
  - To comply with the aerobic intervention and to be able to perform the CGT-TT.
- Dyspnoea caused by heart or lung diseases (e.g. chronic obstructive pulmonary disease (COPD))
  - Having habitual dyspnoea would interfere with the result from the GCT-TT. For instance, testing cardiorespiratory fitness with the GCT-TT when the patient is having acute exacerbation of COPD, will result in a misleading conclusion.
- Aphasia or dementia interfering with the physical examinations
  - Patients with a diagnosis of dementia at hospital admission (e.g. indicated by a score ≤23 of 30 points on the Mini-Mental State Examination (141)) were not invited into the study.
  - To perform the GCT-TT and to understand the purpose of the study the patients must be able to speak and understand/remember instructions.

Study intervention

Since no optimal HIIT protocol yet exist (48), we chose a pragmatic solution in our RCT (study IV) and designed the intervention as simple, motivating, not time-consuming, realistic, and easy to perform during daily living routines for individuals with lacunar stroke.

Setting

The exercise programme was performed in the patients´ home environment because most patients in Denmark get a temporary driving ban for 3 months post-stroke. Additionally, half of the study population were still on the labour market, which made it difficult to participate in fixed group session at the hospital. The easy access to exercise interventions would hopefully motivate the patient to continue exercising after study termination.

Exercise modality

Cardiorespiratory exercise was chosen because it reduces disability following stroke and thereby allows patients to carry out everyday activities (4). Aerobic capacity has previously shown to be low in stroke survivors (4) and they roughly have half the aerobic capacity compared to non-stroke individuals (41).

The specific exercise modality was self-chosen assuming it was aerobic exercise and, that the intensity reached the level where the patient was not able to speak comfortably. At the baseline visit, all patients attended a motivational talk with the study coordinator to encourage lifestyle changes. At this visit, they were introduced to an exercise catalogue including suggestions for modes of aerobic exercise (e.g. high knee exercises, stair stepping, brisk walking, stationary bicycling, outdoor cycling, indoor rowing, running, and swimming). Compliance was expected to be higher when choosing a modality, the patient was motivated for. If the patients were interested, we provided them with a stationary bicycle at home.

We chose the HIIT-intervention because evidence showed that HIIT was more time-efficient compared to traditional endurance-based training (67) and it was an effective alternative to MICE in patients with heart disease (65) and in stroke (72). The purpose of the intervention was to achieve higher intensities to optimize stroke recovery (142). Our exercise programme was designed to maximize the time spent at a high HR, having long high-intensity intervals (3-4 minutes), having a workload of 77–93% max HR ~ RPE >15, and with an active recovery (79). Choosing long intervals with rather high intensity was a way of ensuring that the patients reached

the desired intensity, which can be difficult in intervals of only 30 seconds. To time the exercise intervals, the patients wore a stop watch.

Frequency of HIIT

The international minimum recommendations on physical activity for health (2) recommend at least 75 minutes of weekly aerobic physical activity at vigorous-intensity to achieve a beneficial health effect. Therefore, we chose to investigate the effect of 15 minutes per day, 5 days a week of cardiorespiratory exercise as we expected it to be feasible for the patients and thereby applicable in daily practice, assuming it was effective. Besides, the optimal HIIT-protocol on the most beneficial exercise dose has not yet been established (48).

Exercise performance

The 15 minutes of daily aerobic exercise was performed in intervals making the exercise intervention tolerable for patients, whom we anticipated were unfamiliar with high-intensity exercise, pre-stroke. Each session consisted of intervals with 3x3 minutes of exercise separated by 2 minutes of active recovery.

Exercise-intensity

The patients were encouraged to performed aerobic exercise in bouts of high-intensity. They were guided to exercise at an intensity level where they were no longer able to speak comfortably, corresponding to a level of 14–16 on the BORG 6–20 scale (142). This level corresponds to 77–93% of max HR (high-intensity) (64). To determine the speaking comfort, the intervention group were provided with a cue card (a pocket-sized, laminated standardized text passage).

Measurement of exercise-intensity

We chose to use the TT as a guide for exercise intensity which is a subjective assessment tool measuring perceived effort. The TT is easy to use in clinical practice, and studies have showed that it is useful to prescribe exercise intensity (9, 104).

Motivation

For motivational purpose, the intervention group was contacted by telephone, text message, or e-mail on weekly basis to ensure compliance. Furthermore, all patients tracked their exercise sessions by an individual exercise diary.

Safety

Before study intervention the following safety precautions were performed:

- During hospitalisation, all patients were monitored by continuous ECG-recording for 48 hours.
- Blood pressure control to avoid uncontrolled hypertension.
- Assessment of cardiorespiratory fitness (GCT-TT) at baseline was performed at the hospital with a physiotherapist present.
- The study coordinator visited the patient at their home to guide a safe exercise program and to introduce the Talk Test.
- Weekly calls from the study coordinator to ensure compliance and a safe exercise.

Outcomes

Cardiorespiratory fitness level

We chose the power output, registered in Watts from the GCT-TT as the primary outcome at the post-intervention assessment. Please refer to the subsection "Measurement of cardiorespiratory fitness" for arguments.

The GCT-TT was performed by a physiotherapist with neurological rehabilitation expertise, not involved in the study. During study planning, four physiotherapists were introduced, trained, and calibrated in performing the GCT-TT. The purpose was to ensure that each physiotherapist could perform the test on their own and to ensure that the tests were performed identically each time, independent of the physiotherapist. We engaged four physiotherapists in the blinded assessments due to logistic challenges and resources.

Secondary outcomes

Endothelial function

To evaluate the effect of exercise on endothelial function, we used both a non-invasive physiological method of vasoreactivity and a measure of circulating biomarkers in the plasma. To determine the physiological test, we estimated the Peripheral Arterial Tonometry (PAT) using EndoPAT2000 (Itamar Medical Ltd., Caesarea, Israel) previously applied in the Framingham heart study (143). This method provides variables of the reactive hyperaemia index (RHI), and the augmentation index (AI). The RHI is the post-to-pre-occlusion signal ratio in the occluded arm compared to the same ratio in the control arm and corrected for baseline vascular tone of the occluded arm (144). According to the user manual of the EndoPAT2000 device, a recommended cut-off value for normal endothelial function is a RHI score >1.67.

The AI is a measurement of arterial stiffness and a lower score is a result of greater elasticity of the arteries. The procedure of measuring EndoPAT has been described previously in a study evaluating the validity of the repeated measurement of endothelial function in patients with acute stroke (145). This study showed moderate to substantial correlation on the day-to-day reliability of endothelial function in stroke patients. The intraclass correlation coefficient (ICC) with 95% confidence interval (CI) for RHI in stroke patients was: 0.56 [0.20-0.79], for the AI it was: ICC: 0.95 [0.89-0.98] (145).

Physical activity

Following stroke, there is an interest to increase physical activity to improve independence of everyday life (40). We chose to measure physical activity both subjectively by a questionnaire physical activity scale (PAS2) and objectively by an accelerometer (AX3). We used the PAS2 to evaluate pre-stroke physical activity, to investigate if the patients adhered to the recommendation on physical activity pre-stroke (study III). Also, to assess physical activity post intervention (study IV).

The PAS2 questionnaire is developed in Denmark to evaluate physical activity and sedentary behaviour in the adult Danish population (146). It includes nine questions in total, six questions focus on daily time spent on: sleep, sitting down at work, standing/walking at work, heavy physical work during working hours, active commuting, and sedentary behaviour, and three questions address time spent weekly on: light-intensity, moderate-intensity, and vigorous-intensity activity during leisure time (146). To report the average duration of activity per day, the scores from the

three leisure-time activities were divided by seven, and then added to the scores from the daily activities. When the total time reported was below or above 24 hours, we added or subtracted time that was not accounted for to the category "light-intensity activity," which has been suggested in a previous study (146). The construct validity of the PAS2 (versus a previous version) was evaluated in 342 healthy Danish adults (146). After minor adjustments in the PAS2 questionnaire, the study concluded that the responders answered the questions as intended. Years later, the criterion validity of PAS2 was evaluated in 40 healthy Danish adults. They found a high association between the PAS2 and the activity diary ($r=0.74$, $p=0.000$) (147). Subsequently, the criterion validity of PAS2 versus combined accelerometery and heart rate monitors was explored in 330 healthy Danish adults (148). The study suggested that PAS2 underestimated the time spent in sedentary behaviour compared to accelerometers and heart rate monitors, whereas, it overestimated the time spent in light, moderate and vigorous physical activity (148).

In addition to the PAS2 we applied accelerometers to assess objective physical activity patterns during daily physical activity. We used a three-axis accelerometer, AX3 (Axivity, York, UK), recording with a frequency of 25 Hz for 8 days in total. This period was chosen as a surrogate for the entire intervention period, as a longer recording period cause skin rashes from adhesion of the devise. The AX3 is a wireless, water resistant accelerometer fixed to the right, anterior thigh, midway between the hip and the knee joint. The AX3 was fitted during the physical assessments at the hospital and returned by mail. The AX3 was validated in healthy individuals with a high specificity and sensitivity to differentiate between everyday activities such as walking, standing, sitting, running, stair climbing and cycling (149).

Mental well-being

To evaluate mental well-being, we used the WHO-5 Well-Being Index as it is a short, self-reported questionnaire evaluating mental well-being and available in Danish (150). The WHO-5 Well-being Index consist of five positive statements which the patient answers on a 6-point Likert Scale. The total score ranges from 0-100 points, where <50 points indicate reduced mental well-being or depression (151). The general Danish population above 15 years of age have an average score of 69 points (152). The WHO-5 Well-being Index is valid as a screening tool for depression and it has been used as an outcome measure in clinical studies, including neurology (150). Also, the WHO-5 Well-Being Index has shown high validity as a screening tool for depression in elderly above 50 years of age (153), and in patients with Parkinson´s disease (154). The test has good

psychometric properties when compared to the health status questionnaire Short Form 36 (SF-36) assessed in the general Danish population (152).

Cognitive function

Cognitive function was measured by The Montreal Cognitive Assessment (MoCA) which is brief screening tool identifying mild cognitive impairments (155). The MoCA consist of nine domains: attention, concentration, executive functions, memory, language, visuospatial ability, conceptual thinking, calculations and orientation. The total score ranges from 0-30 points, and a score ≥26 points is considered as normal cognitive function (155). Its validity has been explored in patients with cerebrovascular disease and it compares equally or favourably to the Mini Mental Status Examination in terms of detecting cognitive impairments and to measure changes over time (156).

Post-stroke fatigue

Only few fatigue questionnaires are available in Danish, we chose to use the generic questionnaire, Multidimensional Fatigue Inventory (MFI-20). It has not been formally validated in a stroke population but it has been used to evaluate post-stroke fatigue in Danish patients with first-time stroke (157) and to evaluate the effect of modafinil on post-stroke fatigue in patients with acute stroke (158). Also, the MFI-20 has been applied to describe normative values of fatigue in the Danish population (159).The questionnaire evaluates the following five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity (160). The total score for each dimension of fatigue ranges from 4-20, with higher scores representing increased fatigue (159, 160). We used a cut-off score ≥12 point in the domain of general fatigue as a measurement of overall fatigue, which was recommended in the original development of the scale (160).

Depression

We measured depression using the questionnaire Major Depression Inventory (MDI). It is a short self-reported questionnaire, including 12 questions and available in Danish. The questionnaire was origanally developed in a collaboration with the World Health Organization (WHO) for diagnostic purpose to the Danish general practice (161), in which it has also been validated (162). The MDI has previously been used in patients with aquired brain injury (e.g. brain tumour, brain infection) (163). The total score ranges from 0-50 and has been shown to be an estimate for symptom severity

(164) with higher score indicating more severe depression (161). A score greater than 20 points indicated mild depression, and a score between 15 and 20 points was interpreted as incipient depression (165). We chose to use this questionnaire, recommended by Danish clinical guidelines of depression and frequently used among Danish general practitioners on clinical suspicion of depression (166), and thus increasing the generalizability in Denmark.

Chronic Stress

We used a relatively new method to measure chronic stress, an algometer (Ull Meter®, Ull Care, Hellerup, Denmark) (167). The Ull Meter is easy to use in clinical practice and it has the size of a whiteboard marker and measures pain threshold on the sternum, expressed as pressure pain sensitivity (PPS) (167, 168). With the patient in a supine position, the most sensitive point of the sternum is identified. The Ull Meter is gradually pushed against this sensitive area for 5 seconds, and when the patient experiences discomfort, the pressure is stopped. The PPS is read on a scale from 30-100, with a cut-off point ≥60, correlating with markers of a stress syndrome (169). The result is blinded from the observer until the measurement has finished (167, 168).

The reliability of the PPS was performed by a healthcare professional and evaluated both in healthy individuals, and in patients from a general practice with the diagnosis of e.g. cancer and heart disease (169). Evaluations of reliability showed a high correlation, $r=0.94$, $p<0.001$ in 103 healthy individuals and $r=0.97$, $p<0.001$ in 181 medical patients (169). The PPS is associated with several elements of the chronic stress syndrome: depression score, quality of life scores, and numbers of stress reactions, both in healthy individuals and in patients with ischemic heart disease (167-169). Furthermore, an RCT investigating stress-reducing treatment (acupressure) in patients with ischemic heart disease showed a reduction in PPS was associated with a decline in Major Depression Inventory (MDI) and an increase in mental well-being (WHO-5) (170).

Blood pressure

We measured blood pressure after an overnight fast, aiming for a blood pressure <130/90 mmHg, recommended for patients with a recent lacunar stroke or TIA (31). With the patient in a supine position and after 5 minutes of rest, blood pressure was measured by an automatic blood pressure monitor (Microlife® BP A100/ Microlife® BP A3L Comfort, Widnau, Switzerland).

Body mass index (BMI)

Guidelines recommend health care personnel to screen patients for obesity during hospital admission for stroke (31). Thus, we assessed BMI using a body composition monitor (OMRON HBF-500-E; Kyoto, Japan).

Diabetes/fasting insulin level

Guidelines recommend medical doctors to screen patients for diabetes when admitted to the hospital after TIA or ischemic stroke, to advice patients on lifestyle changes, and to prescribe medication (31). Thus, we assessed fasting insulin concentration in blood samples.

Biomarkers

We have used a stroke related array of biomarkers (endothelial, inflammatory and cardiovascular biomarkers) to estimate the risk of future cardiovascular disease (CVD) based on the complexity of CVD pathogenesis (171). The biomarkers are considered a supplement to other outcome measures, in particular the non-invasive assessments of endothelial function (EndoPAT2000) to detect early subclinical CVD. All blood samples were drawn after an overnight fast, centrifuged at 4000 rpm for 15 minutes at 4ºC within 45 minutes after blood draw and stored at -80ºC until analysis. Technicians blinded to clinical information/randomisation performed the analysis.

Dyslipidaemia, cholesterol. After stroke a rigorous control of lipids is recommended (total cholesterol < 4 mmol/L, LDL< 2 mmol/L and HDL > 1 mmol/L) using statin therapy (31). In our study, patients with a lipid profile above guideline level during admission were treated with statins. Thus, we expected to see a reduction in lipids i.e. LDL and total cholesterol level from baseline to post-intervention assessment, but not necessarily a difference between the groups.

Inflammatory biomarkers. We selected two inflammatory biomarkers for evaluation: Interleukin-6 (IL-6) and tumour necrosis factor (TNF). Both IL-6 and TNF are inflammatory biomarkers which are increased in the brain within 24 hours after an experimental stroke in mice (172), and described to be associated with infarct volume and stroke severity in humans (173). Further, IL-6 is increased immediately post exercise (174), but in aerobic exercise studies the basic levels of IL-6 are decreased in patients with coronary heart disease (175, 176) and during cardiac rehabilitation (aerobic exercise) (177). Exercise is also shown to decrease TNF in patients with cardiovascular risk factors (175, 178) (**Figure 5**).

Endothelial biomarkers. Changes in endothelial biomarkers may in addition to possible changes in the flow mediated dilatation such as measured by EndoPAT, reflect the changes in endothelial function seen in cardiovascular disease or obtained after physical exercise (66). Blood samples were drawn for the analysis of vascular endothelial growth factor (VEGF), vascular cell adhesion molecule 1 (VCAM-1), intercellular Adhesion Molecule 1 (ICAM-1), and E-selectin. Increased levels of VCAM-1, ICAM-1, and E-selectin have been associated with small vessel disease (179), increased arterial stiffness in healthy adults (180), and cardiovascular mortality in older adults (181). In patients with cardiovascular risk factors, aerobic exercise reduces the level of VCAM-1 and ICAM-1 (175, 182), while resistance training does not seem to have a similar effect (183). Furthermore, aerobic exercise also decreases VEGF in patients with cardiovascular risk factors (177, 184) whereas there is insufficient evidence that physical exercise will reduce E-selectin in patients with cardiovascular disease (178) (**Figure 5**).

Cardiovascular biomarkers. We chose to measure the following three cardiovascular biomarkers: pro-adrenomedullin (pro-ADM), pro-atrial natriuretic peptide (pro-ANP), and copeptin. Pro-ADM and pro-ANP regulate vascular tone (vasodilators) and blood pressure. They are both prognostic markers of functional outcome in the acute phase of stroke (185, 186). In a previous cohort study, a high level of pro-ADM was associated with reduced functional outcome in patients with ischemic stroke (185), and in another observational study, the concentration of pro-ANP increased with increasing severity of stroke (186). A recent study showed that pro-ADM and pro-ANP plasma levels decreased after supervised endurance exercise twice a week for 4-6 months in patients with heart failure (187, 188). Furthermore, the study showed that pro-ADM and pro-ANP decreased in the patients who benefitted the most from the exercise program (187).

Copeptin is a surrogate biomarker for antidiuretic hormone which participates in the regulation of fluid balance in the body. Because the antidiuretic hormone has a short life time in humans, copeptin is often measured (189). A previous study showed that the antidiuretic hormone and copeptin were both elevated in patients with ischemic stroke and the elevation was correlated with increased stroke severity (190, 191). According to a systematic review, there is a lack of knowledge regarding the effect of exercise on copeptin investigated in patients with heart failure (188). In fact, only one study was available, and they did not find any changes after exercise (192) (**Figure 5**).

Inflammatory biomarkers

[IL-6]: short-term ↑ during aerobic exercise, but a long-term ↓ after aerobic exercise in patients with coronary heart disease (175,176) and after rehabilitation for cardiac surgery (177)

[TNF]: ↓ after aerobic exercise in patients with coronary heart disease (175,178)

Endothelial biomarkers

[ICAM-1] & [VCAM-1]: ↓in patients with cardiovascular risk factors after aerobic exercise (175, 179)

[VEGF]: ↓in patients with cardiovascular risk factors after aerobic exercise (177, 184)

[E-selectin]: insufficient evidence of exercise efficacy in patients with cardiovascular risk factors (178)

Cardiovascular biomarkers

[Pro-ADM] & [Pro-ANP]: ↓in patients with heart failure after endurance training (187, 188)

[Copeptin]: limited literature available on efficacy of exercise in patients with cardiovascular disease. Only one study in patients with heart failure which did not show effect on Copeptin (188, 192)

Figure 5. Biomarkers response to physical exercise
The major part of the studies is done in patients with cardiovascular disease.

Statistics

Sample size

To comply with the rating "good" in the COSMIN checklist (consensus-based standards for the selection of health measurement instruments) for reliability studies (193), we aimed to include at least 60 patients in our study.

In the RCT we calculated a sample size based on the primary outcome (GCT-TT) using a two-tailed alpha level of 0.05 and a power of 80%. To detect a meaningful average difference of 23 W (SD: 37 W) we needed a sample size of 84 patients (42 in each group). To allow a dropout rate of 15% we aimed to include 100 patients. This power calculation was used in both study III and study IV, as the cross-sectional study (study III) is based on the baseline values from study IV (RCT).

In the reliability study (study I) test-retest data was compared using a paired t-test with mean and standard deviations. Relative reliability was assessed using interclass correlation coefficient ($ICC_{2.1}$) with 95% confidence interval (95% CI) and absolute reliability was calculated to provide clinicians with a 95% assurance of the measured change (in Watt) that represented a real change beyond that expected from measurement error – both for groups and individuals. On group level, the standard error of measurement (SEM) was calculated using the error component from ANOVA (√Error Mean Square) and with 95% CI (SEM_{95}) using (SEM × 1.96). On the individual level, the smallest real difference (SRD) was calculated by (SEM × 1.96 × √2).

In the cross-sectional study (study III), we described data as means with standard deviations (SD) to characterize the study population, to report post-stroke health profile, and to evaluate adherence to recommendations on physical activity. We also evaluated correlations between pre-stroke physical activity and risk factors for stroke using a linear multiple regression.

In the RCT (study II & IV), we used an intention-to-treat approach. Data, from patients with complete outcome data, were analysed according to the group of randomisations, independent of patient compliance. All available data from each patient were included in the analysis, even though the patient did not have all observations. Missing data were not imputed. To compare demographics, baseline characteristics, and within group changes we used a t-test for continuous variables, Wilcoxon signed rank test for ordinal variables, and Fisher´s exact test for proportions. To evaluate changes between the groups, we used the ANCOVA for continuous variables, the Mann-Whitney test for ordinal variables, and Fisher´s exact test for proportions.

In the study protocol, we expected to use a baseline constrained mixed effect model (cLDA) but ended up using the ANCOVA model for practical reasons, and because in a study with baseline and one post-intervention assessment and no missing values or only follow-up assessment values missing, the ANCOVA model and constrained longitudinal data analysis (cLDA model) yield equal results (194).

Before analysis, all variables were tested for normal distribution by histograms and QQ-plots, and if necessary logarithmic transformed. All data were calculated and given as mean difference with 95% CI and a two-tailed alpha with a significance level at $p < 0.05$. Data was calculated using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) and IBM SPSS statistics (version 19.0 and version 22) (Armonk, NY).

Results

This thesis includes four manuscripts; a reliability study, a study protocol, and two studies including the first results from the trial. The first manuscript was a methodological study investigating feasibility, reliability, and measurement error of the Graded Cycling Test with Talk Test (GCT-TT). To test the feasibility, we included 80 in- and out patients with lacunar stroke, who performed a test-trial prior to the test re-test session. Fifteen could not complete the test-trial, and five patients were excluded due to varies reasons (2 patients were diagnosed with lobar stroke, 1 patients had COPD, 1 patient had ischemic pain in the legs and 1 patient experienced a bicycle defect). In the final test-retest analysis we included sixty patients with a mean age of 67 (range 44-85) years. Data showed that GCT-TT was feasible in patients with lacunar stroke and it had a high test-retest reliability at the intensity level where the patient was no longer able to speak comfortably (TT-). At the level of TT-, the patients had a mean score on GCT-TT of 114.8±37.0 W in test 1, and 114.0±35.6 W in test 2 (**Table 1 and Figure 6**). The intra class correlation coefficient ($ICC_{2.1}$) was 0.97 [0.95-0.98]) at the intensity level of TT-. Furthermore, the GCT-TT had a minor measurement error which is important in clinical practice to provide clinicians with the true measurable change. On group level, with 95% certainty the standard error of measurement (SEM_{95}) was 12.9 W. This means, that the patients on group level needed to improve more than 12.9 W to obtain a real change in GCT-TT power output. On an individual level, the change in the smallest real difference (SRD) needed to be above 18.3 W (corresponding to 2 steps (30 W) in the GCT-TT protocol) to represent a real clinical change (**Table 1**). The high reliability and minor measurement error of TT- indicated that the GCT-TT was a well-suited outcome measurement of cardiorespiratory fitness in lacunar stroke rehabilitation.

	Test 1 (W) Mean ± SD	**Test 2 (W) Mean ± SD**	**Diff ± SD (W)**	**$ICC_{2.1}$ (95 % CI)**	**SEM (W)**	**SEM_{95} (W)**	**SRD (W)**
TT-	114.8 ± 37.0	114 ± 35.6	0.8 ± 9.3	0.97 [0.95-0.98]	6.6	12.9	18.3

Table 2. Absolute and relative reliability of Graded Cycling Test with Talk Test
Abbreviations: TT-: The intensity level where the patients were no longer able to speak comfortably, W: Watt, SD: standard deviation, ICC: interclass correlation coefficient, CI: confidence interval, SEM: standard error of measurement, SRD: smallest real difference.

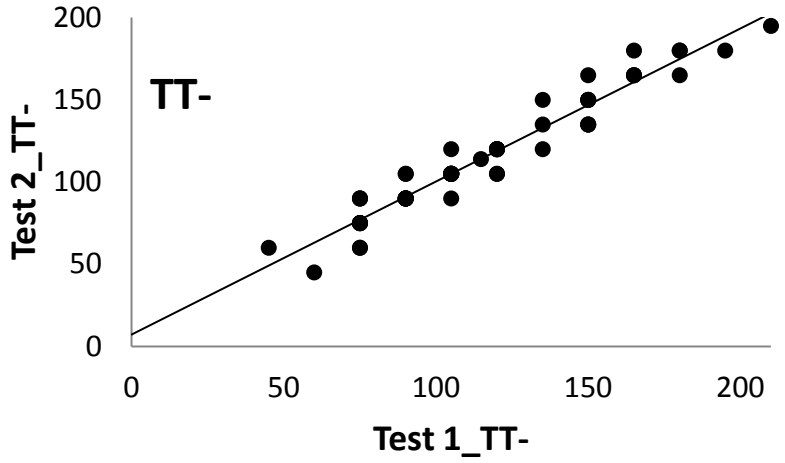

Figure 6. Scatterplot of power output (Watts) for negative Talk Test (TT-) in test session 1 (x-axis) versus test session 2 (y-axis). One dot may represent more than one patient (n=60).

The first study on the results of the trial (study III) was an evaluation of the baseline values on the level of pre-stoke physical activity from the "The effect of aerobic exercise in patients with lacunar stroke". Furthermore, we investigated the association of pre-stroke physical activity level to cardiorespiratory fitness (GCT-TT power output) and risk factors for stroke. The study included 71 patients with lacunar stroke with a mean age 64±9 years. The patients evaluated their pre-stroke physical activity level using the self-reported questionnaire, physical activity scale (PAS2). In total, 56 patients (79 %) adhered to the international minimum recommendations of weekly physical activity (150 minutes of moderate-intensity activity, 75 minutes of vigorous-intensity activity, or an equivalent combination of the two) to reduce risk of lifestyle associated disease (**Figure 7**). Although, our study population were physically active pre-stroke, only 25 patients (35 %) engaged in vigorous-intensity activity on weekly basis.

Evaluating the association between pre-stroke physical activity and cardiorespiratory fitness (GCT-TT power output), sex was a significant predictor, showing that men had a GCT-TT power output 49W higher than women ($p < 0.05$). Also, a previous history of hypertension was associated with a decreased level of physical activity pre-stroke. Patients with a previous history of hypertension did nearly 6 hours/week less of moderate/vigorous activity pre-stroke, compared to patients without a previous history of hypertension.

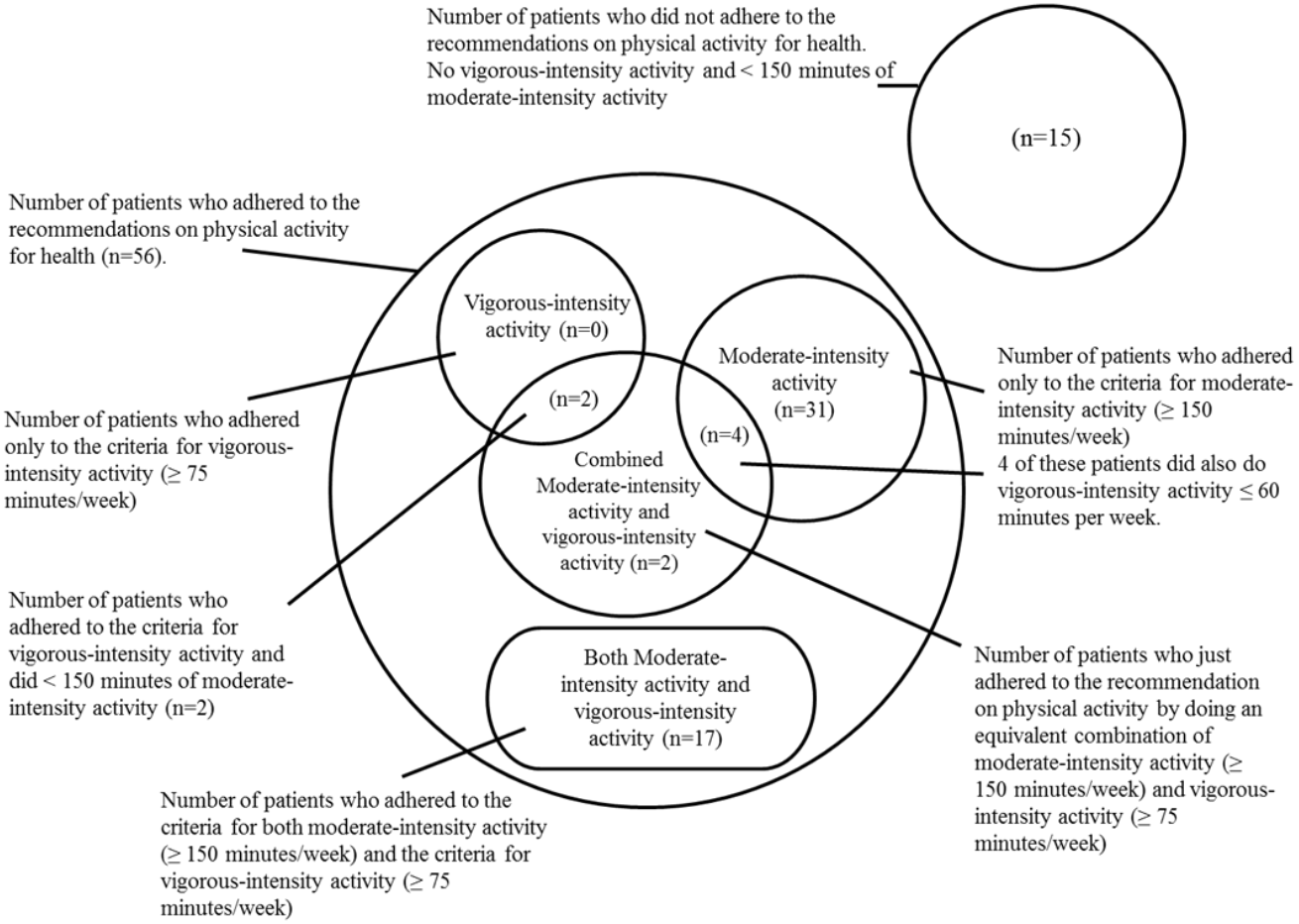

Figure 7. Self-reported engagement in physical activity, pre-stroke.

Figure 7 shows a total of 56 patients adhered to the recommendations on physical activity for health by performing either moderate-intensity activity (≥150 minutes/week), vigorous-intensity activity (≥75 minutes/week) or an equivalent combination

In the HITPALS study (study II & IV), we evaluated the effect of 12 weeks of home-based high-intensity interval training (HIIT) versus usual care, in patients with lacunar stroke, on cardiorespiratory fitness (GCT-TT power output), on general well-being (post-stroke fatigue, chronic stress, depression, mental well-being, cognition), on endothelial function, and in biomarkers (lipids, endothelial biomarkers, inflammatory biomarkers and cardiovascular biomarkers). We included 71 patients in total, 8 dropped out and 31 patients were randomised to the intervention group and 32 patients in the usual care group. We found that home-based HIIT was feasible and safe in patients with lacunar stroke. We succeeded in engaging significantly more

patients in the intervention group to perform vigorous-intensity activity from baseline to post-intervention assessment (**Figure 8**). In addition, the intervention group spent significantly more time (hours/week) on vigorous-intensity activity than the usual care group (p=0.045). The intervention group went from spending median 0.0 [range: 0.0;2.0] hours/week at baseline to 2.0 [range: 0.0;3.0] hours/week at the post-intervention assessment, while the usual care group went from spending median 0.0 [range: 0.0;2,4] hours/week at baseline to 0.6 [range: 0.0;2.0] hours/week at the post-intervention assessment (**Table 3**).

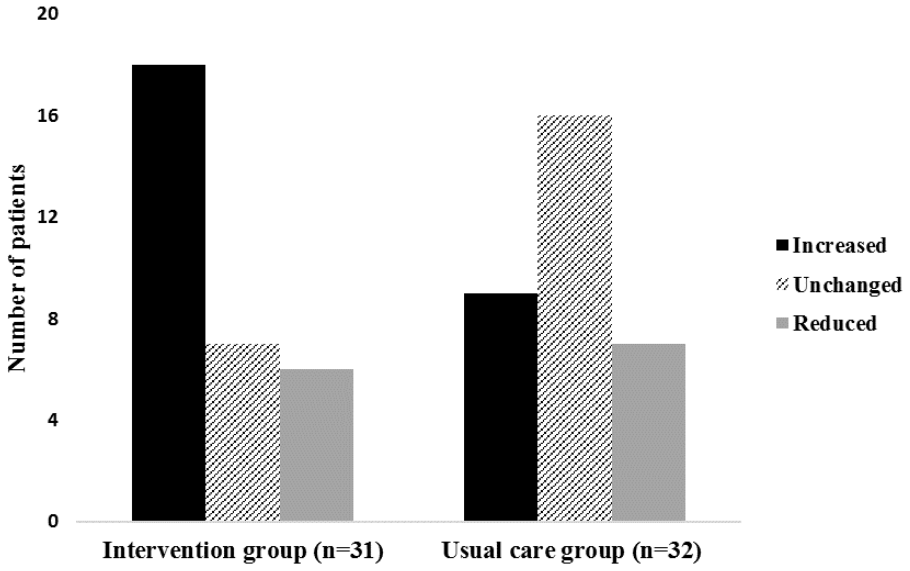

Figure 8. Vigorous-intensity activity at baseline and at the post-intervention assessment, for both groups.
The figure shows the number of patients in each group who either increased, did not change or reduced their engagement on vigorous-intensity activity from baseline to post-intervention assessment.

More patients from both the intervention group and from the usual care group adhered to the international minimum recommendation on physical activity at the post-intervention assessment compared to baseline. In total, 92% of the study population adhered to the recommendation on physical activity for health at the post-intervention assessment, compared to 78% at baseline. Furthermore, 71% of the patients in the intervention group engaged in vigorous-intensity activity at the post-intervention assessment compared to only 32% at baseline, whereas the usual care group only increased their engagement in vigorous-intensity activity from 44% at baseline to 50% at the post-intervention assessment (**Figure 9**).

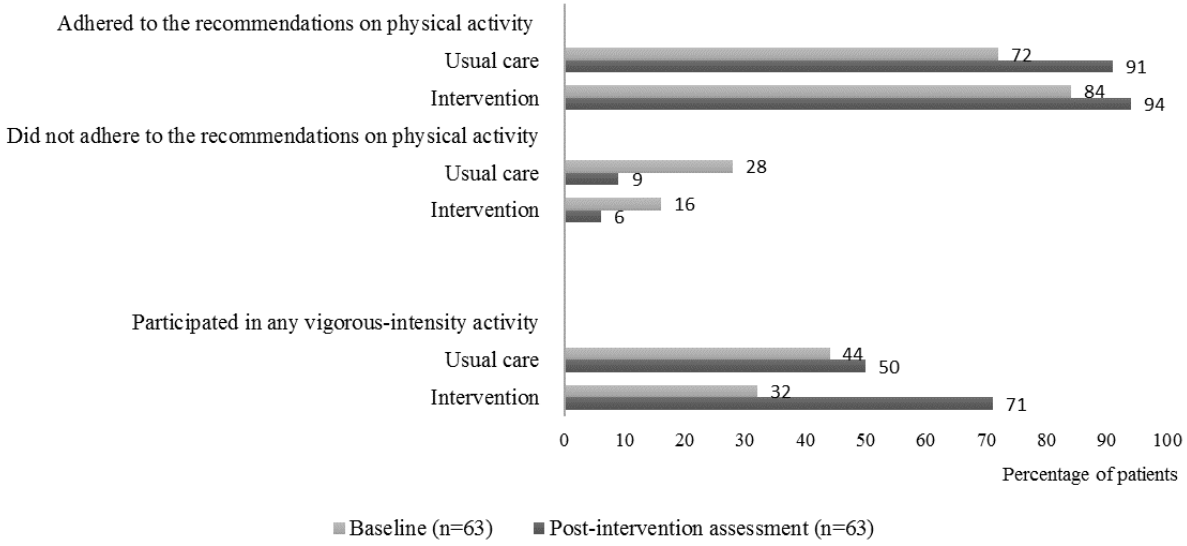

Figure 9. Change in adherence to the international minimum recommendations on physical activity for health, from baseline to post-intervention assessment in both groups.

The patients adhered by doing either vigorous-intensity activity (≥ 75 minutes per week) or moderate-intensity activity (≥150 minutes per week) or an equivalent combination. Furthermore, percentage of patients from both groups who participated in any vigorous-intensity activity at baseline and at the post-intervention assessment.

Regardless of this increased activity in the intervention group from baseline to post-intervention assessment, the results were not translated into a significant improvement in cardiorespiratory fitness (GCT-TT power output), in general well-being or in cardiovascular function within the first three months (**Table 3**). A significant effect was observed between the groups in some of the biomarkers (insulin (p=0.048), ICAM (p=0.006) and VCAM (p=0.024) (**Table 4**). The changes were however small, and not clinically relevant.

	Intervention		Usual care		Difference between groups from baseline to post-intervention assessment		
Variable	**Baseline** (n=31)	**Post-intervention assessment** (n=31)	**Baseline** (n=32)	**Post-intervention assessment** (n=32)	**Difference in change**	**95% CI**	**p***
Primary outcome							
♣GCT-TT, W, (mean ± SD)	118.5±43.1	126.2±46.3	119.5±44.0	126.2±47.9	0.90	-13.9-15.7	0.90
Secondary outcomes							
Post-stroke fatigue, points (mean ± SD)	10 ± 5	11 ± 5	11 ± 3	10 ± 4	1.3	-0.4-3.1	0.13
▲Chronic stress, points (mean ± SD)	62 ± 16	59 ± 15	57 ± 16	55 ± 17	0.7	-5.7-7.1	0.83
Depression, median [IQR]	5 [1;10]	6 [3;13]	9 [4;12]	7 [4;15]			0.86†
Mental well-being, points (mean ± SD)	65 ± 23	69 ± 16	64 ± 18	69 ± 17$	-0.6	-7.7-6.5	0.86
Cognition, median [IQR]	27 [27;29]	29 [28;30]$	28 [26;30]	29 [28;30]$			0.37†
PAS, Physical activity							
- Physical activity, MET (mean ± SD)	39.7 ± 4.7	39.1 ± 4.8	39.3 ± 4.8	40.5 ± 4.2	-1.6	-3.6-0.3	0.10
- Sleep, hours/week (mean ± SD)	52.4±6.7	55.1±8.3	51.6±9.6	52.1±8.6	2.4	-0.7-5.5	0.10
- Sedentary behaviour, hours/week (mean ± SD)	40.7±15.3	42.1±17.9	44.1±18.2	39.6±17.3$	5.1	-1.1-11.3	0.10
- Light activity, hours/week (mean ± SD)	66.6±16.8	62.3±19.1	63.9±19.2	66.8±19.5	-6.2	-14.1-1.8	0.13
- Moderate activity, hours/week (median [IQR])	6.2 [2.6;10.0]	6.0 [2.0;10.0]	5.5 [2.0;8.9]	6.9 [4.4;10.5]			0.28†
- Vigorous activity, hours/week (median [IQR])	0.0 [0.0;2.0]	2.0 [0.0;3.0]$	0.0 [0.0;2,4]	0.6 [0.0;2.0]			0.045†
•Endothelial function							
- RHI, index (mean ± SD)	2.6 ± 1.0	2.6 ± 0.8	2,3 ± 0.5	2.3 ± 0.5	0.1	-0.2-0.4	0.4
Blood pressure							
- Systolic, mmHg (mean ± SD)	149 ± 22	144 ± 18	147 ± 21	141 ± 16$	2.5	-4.9-9.7	0.5
- Diastolic, mmHg (mean ± SD)	85 ± 10	83 ± 10	89 ± 11	84 ± 7$	0.5	-3.2-4.1	0.8
Body Mass Index, kg/m^2 (mean ± SD)	27.5 ± 4.5	27.4 ± 4.3	25.6 ± 3.6	25.4 ± 3.6$	0.3	-0.1-0.6	0.2
**Objective physical activity (hours/day)							
- Activity (incl. cycling, climbing stairs, running and walking), (median [IQR])	0.08 [0;0.38]	0.05 [0;0.5]	0.08 [0;0.66]	0.06 [0;0.6]			0.92†
- Stand/move around, (median [IQR])	1.40 [0.91;2.69]	1.58 [0.89;2.73]	1.63 [1.07;2.79]	1.67 [1;2.69]			0.78†
- Sedentary behaviour (incl. sit/lie), median [IQR]	19.0 [16.9;20.2]	18.9 [17.2;20.6]	18.4 [17.3;19.9]	18.5 [17.1;19.7]			0.62†

Table 3. Results for primary outcome and secondary outcomes measured at baseline and at the post-intervention assessment for both groups.
Difference in change is only provided when a mean difference could be calculated.
IQR: interquartile range, *calculated by ANCOVA, † calculated by Mann-Whitney test (between the groups at the post-intervention assessment), ♣ 29 patients in each group, $ data from within-group analysis are significant, **26 patients in each group, • 30 patients in each group, ▲ 31 patients in the usual care group.

	Intervention		Usual care		Difference between groups from baseline to post-intervention assessment		
Variable	**Baseline** (n=31)	**Post-intervention assessment** (n=31)	**Baseline** (n=32)	**Post-intervention assessment** (n=32)	**Difference in change**	**95% CI**	***p****
Lipids							
- Total cholesterol, mmol/L (mean ± SD)	5.6±1.3	4.2±0.9$	5.5±1.4	4.1±1,2$	0.05	-0.4-0.5	0.8
- LDL, mmol/L (mean ± SD)	3.3±1.3	2.1±0.6$	3.1±1.0•	2.1±0.8•,$	-0.03	-0.4-0.3	0.9
- HDL, mmol/L (mean ± SD)	1.4±0.5	1.5±0.5	1.4±0.4	1.4±0.4	0.10	0.00-0.28	0.3
- Triglycerides, mmol/L (mean ± SD	2.1±1.1	1.3±0.6$	1.7±0.8•	1.2±0.7•,$	-0.06	-0.03-0.2	0.6
Cardiovascular biomarkers							
- Pro-adrenomedullin, nmol/L (median [IQR])	0.57 [0.53;0.71]	0.62 [0.54;0.75]$	0.58 [0.52;0.64]	0.54 [0.54;0.68]			0.58†
- Pro-atrial natriuretic peptide, pmol/L (median [IQR])	64 [50;94]	72 [57;105]$	71 [51,84]	73 [50;93]			0.40†
- Copeptin, pmol/L (median [IQR])	6.5 [4.6;10.2]	6.7 [5.5;10.4]	6.2 [4.6;9.5]	6.7 [4.8;9.7]			0.55†
- Insulin pmol/L (median [IQR])	117 [82;166]▲	106 [82;148]▲	91 [77;138]•	87 [65;103]•,$			0.048†
Inflammatory biomarkers							
- IL6 pg/ml (median [IQR])	1.40 [0.81;3.12]	1.13 [0.82;1.73]$	0.83 [0.71;1.17]	1.10 [0.75;1.52]			0.35†
- TNF pg/ml (median [IQR])	2.27 [1.88;3.53]	2.48 [1.97;2,74]	2.21 [1.89;2.81]	2.32 [1.86;3.20]			0.43†
Endothelial biomarkers							
- ICAM-1 µg/mL (median [IQR])	0.80 [0.64;0.95]	0.78 [0.62;1.26]$	0.82 [0.59;1.08]	0.68 [0.55;0.82]$			0.006†
- VCAM-1 µg/mL (median [IQR])	1.11 [0.60;1.34]	1.16 [0.77;1.52]$	1.06 [0.63;1.46]	0.98 [0.61;1.24]			0.024†
- VEGF pg/ml (median [IQR])	29.8 [25.1;41.7]♠	30.3 [22.5;42.7] ♠	31.2 [25.2;41.2]◊	29.8 [21.1;42.8]◊			0.99†
- E-selectin, ng/mL (median [IQR])	6.22 [4.12;9.88]	5.54 [4.61;7.48]	5.09 [3.60;7.19]	4.76 [4.07;6.58]			0.34†

Table 4. Results for all biomarkers measured at baseline and at the post-intervention assessment for both groups.
Difference in change is only provided when a mean difference could be calculated.
IQR: interquartile range, *calculated by ANCOVA, † calculated by Mann-Whitney test (between the groups at the post-intervention assessment), $ data from within-group analysis are significant, ◊n=25, ▲n=28, ♠n=29, •n=30.

Discussion

Patients with lacunar stroke and no, or only minor, disabilities are usually not considered in need of regular stroke rehabilitation following hospital discharge but may be given advice on lifestyle changes such as exercise. As lacunar stroke is often associated with risk factors of hypertension and diabetes, on which regular physical exercise is beneficial, this lack of a systematic exercise intervention is a potential problem in reducing risk of new stroke. In general, the global population have reduced their level of physical exercise which adds to the individual risk of developing diseases linked to physical inactivity (195). Following stroke, overall physical activity and structured exercise is recommended to improve mobility, to regain or keep the ability to perform everyday activities, and to reduce the risk of a recurrent cardiovascular event (4, 74) . Our overall aim of the studies included in this thesis was to explore how to enhance participation of patients with a lacunar stoke in aerobic exercise. The intervention had to be easily applicable, and continuously adjusted to the progress of exercise capacity, in clinical practice in each of hospital settings, community settings, and at home.

During this series of studies, we explored the feasibility and reliability of an outcome measure (GCT-TT power output) and found it was reliable and with minor measurement error, to monitor exercise effect in patients with lacunar stroke. In addition, we found that the majority of our study population with lacunar stroke (79%) adhered to the recommendations on physical activity, pre-stroke – but few patients performed exercise with high intensity. Lastly, we designed an RCT with a simple, home-based HIIT intervention. The HIIT intervention was feasible and safe and we succeeded to engage patients with lacunar stroke to perform home-based HIIT. Within the first three months we did however not see significant improvements between the groups on cardiorespiratory fitness, general well-being, or in biomarkers at the post-intervention assessment.

Measurements of cardiorespiratory fitness

The golden standard of measuring aerobic capacity (VO_{2max}) is the direct measure of maximal oxygen uptake (86). A downside to this method is that it requires advanced and expensive equipment, which may not be applicable in all clinical or rehabilitation settings. Indirect measures such as a maximal exercise test (91) and the Astrand cycle ergometer test (92) are more likely to be used in clinical practice, and they both estimate aerobic capacity. The maximal exercise test

still requires maximal effort from the patients and the Astrand determines the heart rate response at a sub maximal work rate, to be used to estimate aerobic capacity. In our study we chose to use the GCT-TT power output, a submaximal exercise test to measure perceived effort, registered in Watts. Though not as specific as the VO_{2max} test, the GCT-TT has the advantage that it is applicable in clinical practice in every rehabilitation setting (hospital and community setting), it only requires access to a stationary bicycle, and it is independent of heart rate measurements. The GCT-TT has already been applied in cardiac rehabilitation (107), and studies confirmed that the test has a high reliability and minor measurement errors in patients with ischemic heart disease (107), and we confirmed this in patients with lacunar stroke (196). The TT is a valid and subjective method to evaluate exercise intensity (9). The positive correlation between ventilatory threshold and the TT has been identified in patients with cardiac disease (100-103). Also, the TT is effective in guiding exercise intensity of the patients at home, and by instructing the patients to adjust their exercise intensity to the highest level, matching comfortable speech (104).
We are aware that it would have been optimal to confirm the exercise intensity from each exercise session from every patient with heart rate monitors. However, the aim was to introduce an easy and effective exercise program independent of specific exercise equipment – ready to implement in the patients´ everyday life. This did not include, that the patients must remember to wear a heart rate monitor (a chest strap), to upload data, or to recharge the monitor, as the commercially available heart rate monitors at the initiation of the study had limited memory capacity and limited battery life. Also, during the study planning we did a minor field test of a heart rate monitor attached with electrocardiography electrodes which caused skin rashes following use for more than 3–5 days. Thus, we chose not to measure the exercise intensity by heart rate.

We included both inpatients and outpatients (study I) to test the feasibility and reliability of the GCT-TT as we wanted to use the test in clinical practice within a wide sample of patients with lacunar stroke. Assuming the test was feasible and reliable, this outcome measure may be used as an outcome measure across sectors, both in hospital settings and in the community rehabilitation settings. However, it could be expected that inpatients with a recent lacunar stroke may have a lower power output (watts) in the GCT-TT compared with the outpatients. Consequently, a larger range in power output of the total sample could be expected, leading to a higher ICC value.

Also, our high reproducibility of the GCT-TT power output at the intensity level of TT- was similar to previous findings in patients with ischemic heart disease (ICC: 0.90) (107) and in patients with a recent myocardial revascularisation (ICC: 0.85) (102).

Implementing laboratory results into clinical practice

When exploring the reliability of an exercise test in a laboratory setting, all is standardised to reduce influences from e.g. the environment (like light, temperature, number of people present) equipment (the stationary bicycle, text passage), and the testing procedure (instructions, having a test trial before testing). Having similar conditions when using the test in clinical rehabilitation settings is essential, to be able to trust the results. However, these conditions are difficult to achieve in clinical practice as it requires more time, space and resources. Hence, the results should be interpreted with caution.

We used a test trial to explore feasibility of the GCT-TT procedures prior to the test-retest measurement. We had to confirm that the patients were able to sit on the stationary bicycle, to keep a specific pace and reciting a text passage while they were evaluating the exercise level at which they were out of breath. By introducing a test trial, the patients experienced a learning effect, but they also became aware of finding the level of intensity where they were out of breath, instead of focusing on keeping the cadence and reciting the text passage, which increased the validity of measuring cardiorespiratory fitness. Potentially the test trial could lead to an underestimation of the variability of the test. However, the use of a test trial is a common procedure in the use of exercise test in clinical practice. When measuring functional mobility using the Timed Up and Go test (TUG), it is recommended to perform the test three times, as most patients perform better on their third trial (197).

To determine the importance of a test trial in the GCT-TT we have calculated the mean Watts obtained in the test trial when the patients were out of breath (TT-: 114± 36 W) and compared it with mean Watts from the TT-test 1 (TT-: 115±37 W). These data indicate that there was not a learning effect between the test trial and TT-test 1.

Participants in an exercise study

In contrast to what we hypothesized, we found in the cross-sectional study that 79% of our study population adhered to the international minimum recommendation on physical activity, pre-stroke. The exercise habits may be high in our patient group as a potential bias could be that patients who

are already physically active tend to participate in research studies involving physical exercise, more than patients unfamiliar with exercise. The patients evaluated in the cross-sectional study had all accepted to participate in a following exercise intervention. An additional bias in the cross-sectional study could be the use of the self-reported questionnaire, PAS2. In a previous study patients using the PAS2 had difficulties in recalling the time spent in sedentary behaviour or on light-intensity activity (147). A similar trend was detected in our study as the total daily number of hours in the PAS2 rarely added up to 24 hours. Healthy individuals also tended to overestimate the intensity of activity (147). With attention to the above, the findings from the cross-sectional study should be interpreted with caution, though our results were in line with that of a recent Danish national health survey from 2017 (198). The survey showed that 71% of the Danish population, above 16 years of age, adhered to the international minimum recommendations on physical activity, with men being more active than women (198). Nonetheless, our patient group showed to be physically active, a recent RCT in patients with TIA and symptoms of a minor ischemic stroke, demonstrated that this patient group had a poor cardiorespiratory fitness level one month after stroke onset compared to sex-related and age-related normative values (43). This reduction seemed to be related to a history of either vascular disease or pulmonary disease, and risk factors of stroke such as hypertension, obesity and physical inactivity (43). Thus, it could be relevant to investigate further.

Adherence to physical exercise

Though significantly more patients in the intervention engaged in vigorous-intensity activity at the post-intervention assessment compared to the usual care group, the increased activity was not translated into a significant improvement in the objective measures within the first observation period of three months (study IV). There is currently no consensus on the optimal HIIT protocol to increase cardiorespiratory fitness level in patients with stroke (48), and a dose-response curve on physical exercise is warranted. Our choice of exercise intervention was based on it to be simple, applicable in clinical and daily practice. The absence of immediate effect on outcome variables in the HITPALS study may suggest that the intensity, or the duration of exercise was too low, or it may reflect that we chose to let the almost daily exercise be unsupervised, to make the intervention as lifelike and independent as possible, in contrast to previous HIIT studies involving patients with cardiovascular disease (66). With supervised training, the option of surveillance by heart rate monitors during training would have been possible, surveillance which in this patients group with

potential low computer skills and cognitive challenges was estimated not to be feasible with a home-based training. Another possible reason for the absence of immediate effect may be the choice of outcome variables. Perhaps the GCT-TT protocol may not be sensitive enough as it was based on a step-wise scale, increasing 15 W each minute compared to an exercise protocol based on a continuous scale, and maybe the result would have been different if we have chosen outcomes validated in a stroke population.

Our study differed from previous HIIT studies done in patients with stroke – both regarding the used exercise protocol, population and in the results. Few studies have investigated the effect of HIIT in patients with stroke (72). Only, three studies showed that short-term effect (maximum 4 weeks) of HIIT was superior to MICE (81-83), when it was performed on individual basis, on a treadmill, with gait performance as the primary outcome, and only one study tested the effect on aerobic capacity (VO_{2peak}) (83). More studies are clearly needed which investigate HIIT in stroke patients using the same exercise programme/protocol, exercise modality, exercise length, clinical endpoints, and if the patients were evaluated according to stroke subtype. It may be speculated that patients with a cardioembolic stroke could face problems with heart rate monitoring, and patients with large artery stroke may suffer from peripheral vessel stenosis limiting the training ability.

The exercise program

The most effective exercise approach in stroke rehabilitation remains to be established (40). Our exercise intervention (study IV) was designed to be effective and easy to apply in an everyday life. The home-based HIIT was feasible for our patients with lacunar stroke, confirmed by a low drop-out rate, and with significantly more patients performing vigorous-intensity activity at the post-intervention assessment compared to baseline. Our results, with a home-based physical intervention approach were encouraging compared to the findings in a large international multicentre study (ExStroke), which found no effect of repeated encouragements and verbal instructions on physical activity in patients with ischemic stroke (49). Hopefully, the follow-up data will show that our patients have integrated the HIIT intervention into their daily living, e.g. as a part of their daily commuting to and from work. This would be fantastic as a previous study, the GO-ACTIVE study (199), have showed that daily commuting was at least as effective (on reduced fat mass after 6 months) as moderate-intensity leisure-time in adults with overweight and obesity who previously were unfamiliar with leisure-time exercise.

Secondary outcomes

The RCT (study IV) included secondary endpoints (general well-being, cardiovascular function and biomarkers) which were hypothesis generating or explorative in investigating the impact of aerobic exercise on patients with lacunar stroke.

In contrast to our hypothesis, but in line with previous studies in stroke, we did not find an effect of HIIT on mental well-being, cognitive function, or depression (4). A Cochrane review including only few studies, showed inconsistent results of aerobic exercise and resistance training on well-being and depression (4), however there might be a small trend towards a positive effect on cognitive function (4). Of consideration in interpreting these outcome results, there may be a ceiling effect in this population with lacunar stroke who were able to comply with an exercise programme including a high-intensity intervention. In our study, we saw a ceiling effect, as the patients had a low depression score at baseline (<20 points which was the cut-off score for mild depression) (165), a high score of mental well-being at baseline, almost similar to the Danish adult population (69 points) (152), and a high score of cognitive function at baseline (cut-off score: ≥26 points for normal cognitive function (155)).

There is little evidence that exercise is effective to reduce chronic stress and post-stroke fatigue. Only one study available, showed a small trend towards a positive effect of exercise on chronic stress, however this study was done in rats (134). Insufficient evidence is available on the effect of pharmacological and none-pharmacological intervention to treat or prevent post-stroke fatigue (125). Neither did we find an effect of HIIT on chronic stress or post-stroke fatigue, maybe due to a ceiling effect. Our patients had a low score of post-stroke fatigue at baseline (<12 point which was the cut-off score of fatigue) (160) and a stress level, similar to or below the cut-off value at baseline (≥60 points was the cut-off score) (169).

Previous studies showed that exercise reduced blood pressure (110) and fasting levels of insulin (46) in stroke patients. In our study, both groups received antihypertensive medications, thus the potential effect of the exercise intervention could not be detected. Regarding insulin level, we did see a significant effect of exercise on reduced fasting insulin level in favour of the intervention group, even though the fasting level in both groups were below normal at baseline (<174pmol/L) (200). However, this significant change between the groups was small and not clinically relevant. Similar to other exercise studies in patients with stroke we did not find an effect on BMI (46, 110) or on endothelial function (66). Perhaps a longer duration of exercise intervention would have shown a different result on BMI, and potentially did our patients (both groups) have endothelial

function values representing normal function at baseline (>1.67 according to manufacturer's user manual).

The biomarkers response to exercise has primarily been investigated in patients with cardiovascular disease and few specifically in patients with lacunar stroke. Inflammatory biomarkers (IL-6 (over time) and TNF) decreased after aerobic exercise in patients with coronary heart disease (175, 176, 178). We did not show similar changes in patients with lacunar stroke which could be explained by a low level of inflammation in lacunar stroke compared to patients with cardiovascular coronary heart disease, different exercise interventions applied, or different sensitivity or specificity between the applied commercial biomarker kit. However, we did demonstrate a higher level of both IL-6 (median cut-off value: 0.24 pg/ml) and TNF (median cut-off value: 0.106 pg/ml) at both baseline and at the post-intervention assessment compared to a healthy subject sample (manufacturer´s normative values). This indicate that our sub-group of stroke patients may have a general inflammatory response, and that our exercise intervention did not reduce this level of inflammation.

The endothelial biomarkers (ICAM and VCAM) decreased after aerobic exercise in patients with cardiovascular risk factors (175, 179). We showed a similar effect on ICAM and VCAM, but the results were small and not clinically relevant, and a higher sample size may be required to detect clinically relevant changes. Also, VEGF decreased after aerobic exercise in patients with cardiovascular risk factors (177, 184), a change we could not confirm in our study. However, compared to a healthy subject sample (manufacturer's normative values) we observed a higher level of ICAM (median normal value: 343 ng/ml), a lower level of both VCAM (median normal value: 491 ng/ml) and VEGF (median normal value: 54.5 pg/ml) at both time points (Table 4). These changes could be a sign of endothelial dysfunction, corresponding to what could be expected in patients with risk factors of hypertension and diabetes. Previous data on the effect of exercise on E-selectin is inconsistent, and neither did we detect a significant difference between our study groups.

A decrease in cardiovascular biomarkers (pro-ADM and pro-ANP) after endurance training were detected in patients with heart failure (187, 188), but not in our study, which could reflect that patients with lacunar stroke had no compromised cardiac function. Similarly, only one study was available in patients with heart failure but failed to show effect of exercise on Copeptin (188), and neither did we observe an effect on Copeptin. However, we observed a higher concentration in our cardiovascular biomarkers at both time points compared to a healthy subject sample

(manufacturer´s normative values, pro-ADM median: 0.39 nmol/L, pro-ANP median: 46.1 pmol/L and copeptin median: 3.9 pmol/L) (Table 4). These higher values could be a sign of change in cardiac function or endothelial dysfunction, corresponding to what could be expected in patients with risk factors of stroke.

Strengths and limitations

One possible strength of the HITPALS study (study IV) was that patients had free choice of aerobic exercise modality performed in the patients´ home environment which gave the patients the opportunity to choose the exercise modality they were motivated for, and to exercise whenever appropriate. In contrast to, the supervised group sessions performed on specific days and hours at a designated training facility, likely to interfere with potential fatigue, the usual three-month driving ban, and thus lack of transportation. Concurrently, the free choice of modality could be a potential bias. Patients using a stationary bicycle as their exercise modality, may have been an advantage as they became familiar with the modality and thus potentially performed better at the post-intervention assessment. It has been suggested that submaximal exercise thresholds e.g. ventilatory threshold occur at a relatively lower exercise intensity during incremental exercise tests when using unfamiliar exercise modalities (201). However, it did not seem to be the case in our study. Another strength was the reliability testing of the GCT-TT (study I). Before using the GCT-TT as the primary outcome in a large-scaled exercise study in patients with lacunar stroke, we found the GCT-TT to be reliable and with minor measurement error in this sub-group of stroke patients (196). Also, we considered the use of the TOAST classification to sub-categorize the patient sample to be a strength as the stroke etiology may associate to specific risk factors and influence the prognosis (18).

An obvious limitation of the study was the failure to recruit the power-estimated predetermined number of patients due to the challenge of engaging patients with lacunar stroke in daily physical exercise (study IV). To increase inclusion rate, we made an amendment to the study protocol to recruit patients with lacunar stroke from three stroke units instead of one. However, this amendment was unproductive. The lack of exercise effect on any of the outcomes made it unrealistic to expect significance with only 15 more patients in each group.

Theoretically, the amendment turned the study into a multicenter trial, but generalizability should be made with cautions as only two patients were recruited from each of the collaborating stroke units.

Another limitation in both the reliability study and in the RCT was the skewed sex distribution with more men than women recruited, which reduced the generalisability of the study results. There are several possible explanations for this skewed sex distribution. Firstly, our sample reflects the higher stroke incidence in younger men compared to age-matched women (202). Secondly, men may be more interested in research activities involving physical exercise than women. A recent review showed that women tend to do less leisure-time activities, and at a lower intensity activity than men (195). Another concern of both studies (reliability and RCT) could be selection bias as only patients with an interest in physical activity would volunteer and other eligible patients declined for reasons of lack of time, lack of transportation access, or work obligations (51, 69, 70). Also, in study III, we may have reduced the number of patients who declined to participate, if the patients only were invited to answer the questionnaires.

When informing the patients about the purpose of the study and the importance of physical activity in general, some of the patients from the usual care group felt inspired by the prospect of being able to do something themselves about their situation and thereby engaged in physical exercise. This engagement of the usual care group is a limitation in all exercise studies which is not easily controllable, due to the ethical requirement that all patients must be informed about the purpose and possible benefits of the intervention.

Conclusion and clinical implications

The test-retest reliability study on the Graded Cycling Test with Talk Test (GCT-TT) showed that GCT-TT was a feasible and reliable assessment tool for monitoring exercise effect (registered as power output in Watts) in patients with lacunar stroke. The small measurement error and high relative reliability of the test, makes it a valuable outcome measure in clinical practice. The GCT-TT was user-friendly and not time consuming, which makes it suitable in research settings as well as in clinical settings.

Physical inactivity is one of the major risk factors for stroke, and we hypothesized that patients with lacunar stroke generally did not adhere to the recommendations on physical activity for health, pre-stroke. In contrast to our hypothesis, we found that 79% of our study population adhered to the international minimum recommendation on physical activity – similar to the level of physical activity seen in the general Danish population. Only one third reported to perform physical activity pre-stroke with an exercise intensity sufficient to improve cardiorespiratory fitness. More research is warranted to investigate the possible beneficial effect of vigorous-intensity activity in patients with either lacunar stroke or stroke in general.

In the final study, we investigated the effect of 12 weeks of home-based high-intensity interval training (HIIT) and found that it was feasible and safe in patients with lacunar stroke. We succeeded in engaging more patients with lacunar stroke in vigorous-intensity activity and to perform it for a longer period of time. However, this increase in exercise was not translated into an increase in effect on cardiorespiratory fitness (GCT-TT power output), general well-being, and selected biomarkers after 12 weeks. Further research on the long-term effect of home-based HIIT and possible ways to improve cardiorespiratory fitness after lacunar stroke are warranted.

Based on data presented in this thesis and previous HIIT intervention studies in patients with stroke, HIIT seems feasible and safe to perform. However, studies investigating effect of HIIT in patients with stroke are limited, showing inconsistent results and uses a variety of different HIIT protocols.

Future perspectives

Research supports that cardiorespiratory exercise is effective and recommended as part of the rehabilitation after stroke (4). However, the optimal "exercise pill" or approach in recovery of function and mobility after stroke or stroke prevention, are yet to be found (40). Consequently, we investigated one approach, including unsupervised home-based high-intensity interval training, which was neutral to improve cardiorespiratory fitness. Future exercise studies on the efficacy of cardiorespiratory exercise after stroke may focus on exploring the most effective exercise approach and should be prescribed according to modality (type of exercise), timing (when to initiate exercise), duration (duration of exercise intervention and duration of each exercise sessions), frequency (number of exercise sessions per week), intensity (number of repetitions or intensity level of exercise), and outcome measures (how to evaluate the effect).

The long-term follow-up is still ongoing. This analysis will explore, if there is a difference between the groups, in the number of patients who have kept exercising on regular basis after termination of the HIIT intervention. This will provide an insight in how easy or difficult it is to integrate a home-based aerobic intervention as a routine in daily living after lacunar stroke. Also, we await analysis of the MRI outcome after the 12-months follow-up assessment to investigate changes in terms of cerebral blood flow, new lacunar strokes, white matter lesions and microbleeds.

Another issue to pursue in future studies, may be how to make sustainable lifestyle changes to prevent a recurrent event in patients with lacunar stroke. Previous studies have shown that a combined exercise intervention (aerobic exercise and resistance training) with stroke education have a positive short-term effect on stroke risk factors (blood pressure, total cholesterol and aerobic capacity) in patients with lacunar stroke (203). Also, the long-term effect of this combined intervention showed fewer strokes and/or TIA events within a 3.5 year of follow-up (204). Based on our findings, with a neutral result after unsupervised exercise, and inspired by previous studies, with a combined exercise and education intervention, we plan to explore a supervised exercise intervention combined with education. This group intervention may address patients with lacunar stroke and TIA who is unfamiliar with exercise and unaware of risk factors for stroke. We aim to improve their stroke risk profile by doing supervised aerobic exercise in a safe environment with piers who they share history with, in combination with education on stroke risk factors.

Of further interest, studies investigating if it requires a specific exercise approach following stroke, depending on stroke etiology. Many stroke studies do not describe the cause of the stroke, e.g. cardioembolic, carotid artery stenosis, large artery stroke or lacunar stroke. How do we know which of the sub-groups will befit the most from aerobic exercise? And are patients with stroke due to cardiac disease more reluctant to do aerobic exercise? Does one sub-group of stroke patients need a resistance training approach, and the other an aerobic approach to recover from stroke, and to prevent new incidents. These questions may be hypotheses for future studies.

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Manuscripts

Introductory remarks for study I: *"Graded Cycling Test with Talk Test" Is a Reliable Test to Monitor Cardiovascular Fitness in Patients with Minor Stroke.*

The purpose of this reliability-study was to investigate test-retest reliability of the Graded Cycling Test with Talk Test in patient with lacunar stroke and to assess measurement error of the test. Furthermore, to explore the feasibility to provide valuable information regarding practical application to this target group prior to using the measurement as the primary outcome in an RCT.

Introductory remarks for study II: *Home-based aerobic exercise in patients with lacunar stroke: design of the HITPALS randomized controlled trial.*

The purpose of this protocol study was to describe how we designed and planned the RCT. The short-term aim of the study was to evaluate 12 weeks of early initiated home-based high-intensity interval training in patients with lacunar stroke in addition to usual care versus usual care, only. Furthermore, the long-term aim (5 years) was to evaluate improvements in risk profile on cardiovascular event, including stroke recurrence.

Introductory remarks for study III: *Self-reported physical activity and health profile in patients with lacunar stroke".*

Inactivity is one of the greatest risk factors for stroke, and we wanted to explore whether patients with lacunar stroke adhered to the international minimum recommendation on physical activity for health prior to stroke, by assessing their self-reported physical activity. Furthermore, we assessed the patients´ health profile to explore the effect of self-reported physical activity on cardiorespiratory fitness and other well-known risk factors for stroke.

Introductory remarks for study IV: *"Effect of home-based high-intensity interval training in patients with lacunar stroke: a randomized controlled trial".*

Cardiorespiratory fitness is recommended after stroke to improve mobility and prevent cardiovascular disease. This RCT was conducted to evaluate whether 12 weeks of home-based high-intensity interval training, combined with usual care versus usual care only, was feasible and may improve cardiorespiratory fitness, general well-being, cardiovascular function and biomarkers in patients with lacunar stroke.

"Graded Cycling Test with Talk Test" Is a Reliable Test to Monitor Cardiovascular Fitness in Patients with Minor Stroke

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Background: Physical exercise is generally recommended as part of life style changes post stroke. Monitoring cardiovascular effects may help motivate patients for further exercise, and can be an instrument to assess intervention effects in clinical trials. In 1 of 4 stroke patients, the heart rate variability may challenge currently used cardiovascular monitoring. The Graded Cycling Test with Talk Test is a submaximal exercise test independent of heart rate variability, shown reliable for patients with cardiac disease. *Methods:* Patients diagnosed with lacunar stroke according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria performed an incremental exercise test on a stationary bicycle with a 15 W (watt) increase in workload every minute. Toward the end of each incremental step, the patients recited a standardized text passage and subsequently were asked: "Are you still able to speak comfortably?" The test was stopped when the patients were no longer able to speak comfortably. Two consecutive tests were performed separated by 1 hour rest. *Results:* Sixty patients completed the study. The intraclass correlation coefficient ($ICC_{2.1}$) was as follows: .97 [95% CI: .95-.98] with only a minor measurement error: 12.9 W for groups of patients (standard error of measurement, SEM_{95}) and 18.3 W for individual patients (smallest real difference). *Conclusion:* The "Graded Cycling Test with Talk Test" is feasible and reliable for monitoring exercise effects in patients with lacunar stroke. The high $ICC_{2.1}$ and small measurement error suggest it to be a valuable outcome measurement in clinical practice. **Key Words:** Graded Cycling Test—lacunar stroke—outcome assessment—reproducibility of results—Talk Test.

Introduction

Physical exercise is generally recommended as one of the life style changes for poststroke patients to reduce risk of cardiovascular events or recurrent strokes.[1] Patients with a lacunar stroke, caused by small vessel disease (SVD), have a threefold greater risk of subsequent new stroke.[2,3] Evidence supports that physical activity after a stroke can lower the blood pressure and improve cardiovascular fitness.[4] A test of aerobic capacity is necessary to assess the short-term effects of exercise intervention on stroke patients. In 20%-30% of patients with stroke, the heart rate variability may be affected by atrial fibrillation,[5,6] and likewise in patients treated with heart rate regulating medication, such as beta blockers. This may challenge the outcome of exercise testing which is

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based on measurement of heart rate. Furthermore, the direct measurement of maximal aerobic capacity is strenuous for the patient and requires advanced equipment and expertise, and submaximal exercise tests such as Åstrand Test[7] are often based on heart rate measurements. Consequently, a simple, standardized, submaximal exercise test which is independent of the heart rate would be more suitable for use in the clinic. The Graded Cycling Test with Talk Test is a submaximal exercise test feasible and reliable for use in patients with cardiac disease.[8] We thus hypothesize that the Graded Cycling Test with Talk Test is also feasible and reliable for patients with a lacunar stroke. It is essential to establish whether this is the case as stroke patients may perform differently from cardiac patients as stroke patients are older and may suffer from stroke sequelae. So far there are no studies validating the Graded Cycling Test with Talk Test against direct measurement of maximal oxygen consumption or the ventilatory threshold in any patient group. The Talk Test by itself has, however, been used with a variety of incremental exercise test protocols—i.e., during treadmill walking,[9-11] corridor walking,[10] and stationary bicycling.[12-14] Regardless of exercise mode and protocol, the last positive, or in most cases the equivocal, stage in the Talk Test has been found to correlate with the ventilatory threshold in elite and recreational athletes,[12,15] sedentary and healthy adults,[9,15,16] as well as in cardiac patients.[10,11,13,17] Further, the Talk Test is responsive to changes in aerobic capacity following blood donation and aerobic training.[9] The current study investigates feasibility and reproducibility in patients with a lacunar stroke, as this is the group of patients who are most likely to engage in physical exercise immediately post stroke.

Methods

The study was approved by The Danish Data Protection Agency (ID: 2012-58-0004) and The Research Ethics Committee in the Capital Region of Denmark (H-1-2014-FSP-031) according to the Declaration of Helsinki of 1964, as revised in 2008. All participants gave written informed consent before enrollment.

Participants

The study was designed as a test–retest study, including patients with lacunar stroke from Herlev Gentofte Hospital from October 1, 2014 to May 1, 2015. We aimed to include at least 60 patients, in accordance with the COSMIN checklist (**CO**nsensus-based **S**tandards for the selection of health **M**easurement **IN**struments) for reliability studies.[18] The patients included in the study were patients with a first time lacunar stroke (24 patients), patients with a recurrent lacunar stroke (21 patients) verified by acute computed tomography (CT) or magnetic resonance imaging (MRI) scans, or patients suffering from symptoms of lacunar stroke with evidence of only old lacunar infarcts but no new lesion verified by CT or MRI scans (15 patients). Both inpatients and outpatients were included in the study to ascertain if the Graded Cycling Test with Talk Test was applicable during the entire rehabilitation period. Inpatients were recruited consecutively from the stroke unit. Outpatients were recruited either shortly after discharge (n = 12) or from patients attending their 3 months control visit (n = 8), or their later follow-up visit at the stroke unit (1 patient at 6 months and 2 patients at 12 months).

Selection Criteria

The lacunar infarct was verified by clinical examination and CT or MRI scans, and defined as small infarcts (<2 cm diameter, in the acute stage) according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria for SVD stroke.[19]

Inclusion criteria were as follows: age more than 18 years; ability to speak and read Danish; and ability to give informed consent. Exclusion criteria were as follows: previous large artery stroke; symptoms or comorbidities in the musculoskeletal system, which could hinder exercise testing on a stationary bike; dyspnoea caused by heart or pulmonary disease; and aphasia or dementia which could hinder completion of the Talk Test.

Test Protocol

The test leader (R.S.K.) was formally instructed in the test procedure by an experienced tester who had conducted more than 200 tests. A pilot study was done prior to the main study, including 5 healthy subjects and 5 patients with lacunar stroke. The purpose of the pilot study was to practice the test procedure including observations and instructions. All patients performed a test trial prior to the day of reliability testing to get familiarized with the testing procedure and thus minimize the risk of bias due to learning effect. For the reliability study, the cycling test was performed under identical conditions twice on the same day. The 2 test trials were separated by 1 hour of rest, during which only water was offered to the patients. The test was performed in an undisturbed examination room with daylight illumination and an average temperature of 20°C on a stationary bike (Monark 928E-G3, Vansbro, Sweden). The bike was electronically braked and calibrated daily before testing. The patients wore a heart rate monitor (Polar FS2c, Kempele, Finland) around the chest. During the test, the current heart rate was displayed on a computer, not viewable for the patients. The heart rate was monitored (in beats per minute, bpm) to ensure that the increasing workload during the cycling test resulted in an appropriate increase in exercise intensity.

The patients cycled for a period of 2 minutes at a low intensity (15 W [watt]), at 60 rounds per minute (rpm). The intensity was then increased automatically by 15 W

every minute until the end of the test.[8,20] During the last 10 seconds of every minute, the patients recited a Danish standardized text passage consisting of 30 words.[8] Subsequently, the patients were asked the following question: "Are you still able to speak comfortably?", and were given the choice of 3 responses: "Yes," "unsure," and "no," corresponding to Talk Test+, Talk Test±, and Talk Test–, respectively. The patients could answer "yes" and "unsure" as many times as they felt appropriate, but when answering "no" the test was stopped. Except for this communication, they were not allowed to talk during the test. Using this procedure, all patients would always use "yes" and "no," whereas the answer "unsure" was only used by some patients and not necessarily on every test occasion. Consequently, only the answers "yes" and "no" were used in the analysis of reliability. To minimize bias of being observed or developing performance anxiety, the patients were informed that the purpose of the test sessions was to examine the test, not their aerobic fitness level.

Statistical Analysis

Mean and standard deviations (SD) were calculated for each level in the Talk Test (Talk Test+, Talk Test±, and Talk Test–). A paired *t*-test was used to assess if the results of the 2 test sessions were significantly different from each other, as this could indicate systematic bias.

Relative reliability was assessed using intraclass correlation coefficient ($ICC_{2.1}$) with 95% confidence interval (CI). Absolute reliability was calculated to provide a precision estimation of the Graded Cycling Test with Talk Test and to provide clinicians and researchers with an estimation of the magnitude of change measured in the units of the test (W), and with a need of 95% assurance that the change occurring represented a real change, beyond that expected from measurement error.[21] For this purpose, a two-way analysis of variance (ANOVA; random model) was applied and the standard error of measurement (SEM) was calculated using the error components from the ANOVA ($\sqrt{}$Error Mean Square).[21,22] The smallest real difference (SRD) was calculated ($SEM \times 1.96 \times \sqrt{2}$) as described by Beckerman[23] to estimate the change needed for an individual subject to be 95% sure that the change is real—i.e., in the clinical setting. This corresponds to the minimum difference described by Weir.[21] Moreover, the SEM_{95} was calculated ($SEM \times 1.96$) to estimate the SEM with 95% CI—this is the change needed to exceed the measurement error with 95% certainty for groups of participants—i.e., in research settings.

Data analysis was performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) and IBM SPSS statistics 19.0 (Armonk, NY).

Results

Sixty patients were included in the final test–retest analysis. See Figure 1 for details about exclusion and dropout. Patient characteristics of the 60 patients are provided in Table 1.

All patients used the Talk Test+ and Talk Test– responses and 32 (53%) patients used Talk Test± in test 1 and 33 (55%) in test 2. The test reproducibility of Talk Test+ and Talk Test– is illustrated in Figure 2 and presented in more detail in Table 2. In fact, the reliability of Talk Test– was extremely high as even the lower limit of the 95% CI for the $ICC_{2.1}$ was well above .9, the SEM_{95}

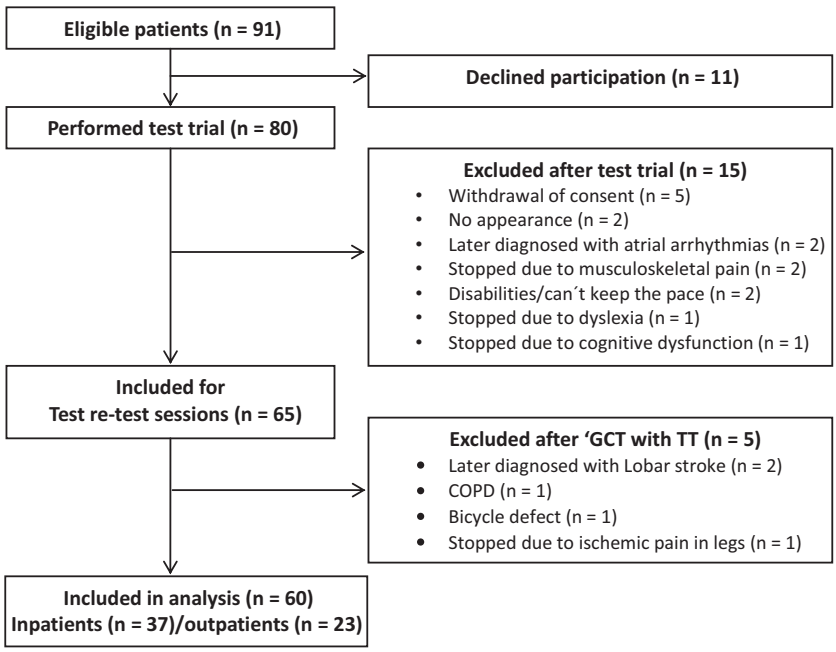

Figure 1. *Flowchart. Abbreviations: COPD, chronic obstructive pulmonary disease; GCT, Graded Cycling Test; TT, Talk Test.*

Table 1. *Baseline characteristics*

Participants, n	60
Women, n (%)	19 (32%)
Age, mean years (range)	67 (44-85)
Inpatients, n (%)	37 (62%)
Number of days between admission and testing	
Inpatients (median, range)	3 (2-21)
Outpatients (median, range)	43 (8-269)
Clinical symptoms on admission	
Paresis/dexterity of the extremities, n (%)	32 (53%)
Visual problems, n (%)	10 (17%)
Dysarthria, n (%)	24 (40%)
Vertigo, n (%)	8 (13%)
Sensory impairments of the extremities, n (%)	24 (40%)
Mobility, walking aids, n (%)	4 (7%)
Social	
Cohabitants, n (%)	45 (75%)
Living alone, n (%)	15 (25%)
Hypertension, n (%)	45 (75%)
Diabetes, n (%)	7 (12%)
Arthritis, n (%)	10 (17%)
Beta blocking agents, n (%)	1 (2%)

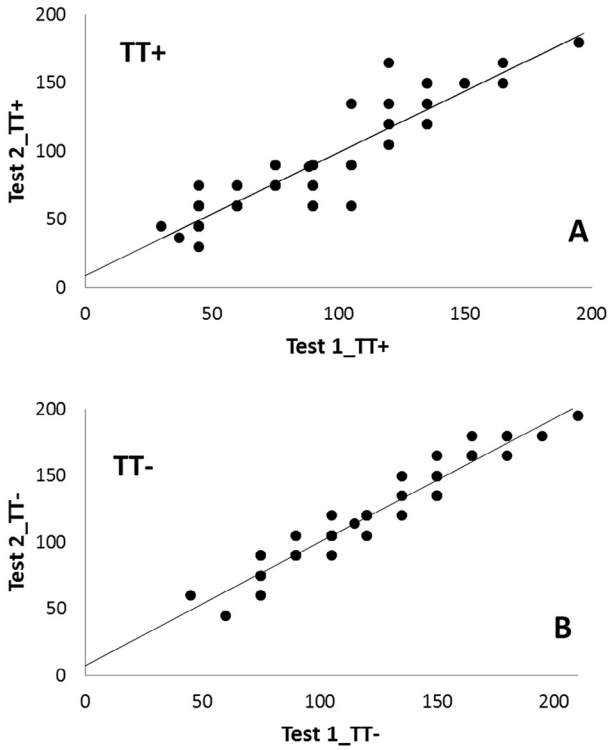

Figure 2. *Scatterplots of power output (watts) for TT+ (A) and TT– (B) in test session 1 (x-axis) versus test session 2 (y-axis). One dot may represent more than one participant (n = 60). Abbreviations: TT+, positive Talk Test; TT–, negative Talk Test.*

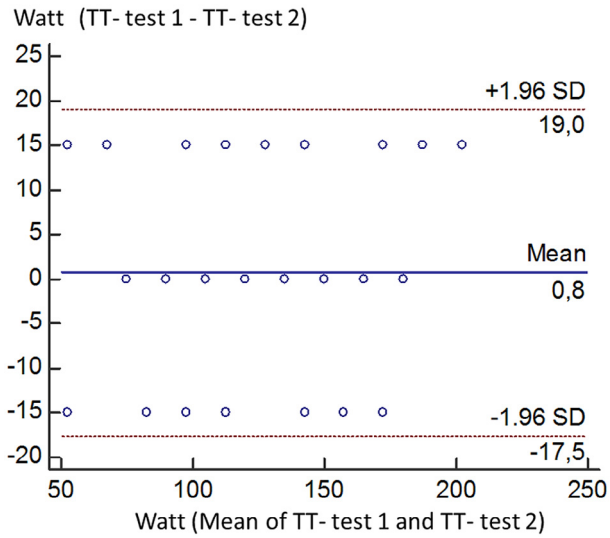

Figure 3. *Bland–Altman plot. The x-axis represents the mean of the power output recorded at TT– in test 1 and the power output recorded at TT– in test 2. This is plotted against the difference between TT– in test 1 and TT– in test 2 (TT– in test 1 minus TT– in test 2) on the y-axis. One circle may represent several patients. The mean difference between TT– in test 1 and TT– in test 2 was .8 W, and no patients exhibited differences exceeding 1 step of the incremental test protocol (15 W). Abbreviations: SD, standard deviation; TT–, negative Talk Test.*

was ≈13 W, and the SRD was 18.3 W—well below 2 steps (30 W) in the incremental test protocol (Table 2).

Further, a Bland–Altman plot confirmed that no heteroscedasticity, no systematic bias, and no variations above 15 W, corresponding to 1 step in the cycling test, were present for Talk Test– (Fig 3).

A small but statistically significant difference in pulse rates at Talk Test– was observed between the 2 test sessions: Session 1: 121 bpm (SD: 19,2); and Session 2: 118 bpm (SD: 17,8) (P = .014). However, the ICC was high ($ICC_{2,1}$: .91[.85-.94]) and an average difference of 3 bpm was not considered clinically relevant.

Discussion

Patients with lacunar stroke tolerated well the Graded Cycling Test with Talk Test, and they also cooperated well to the test protocol. Further, the Graded Cycling Test with Talk Test showed high reliability and minor measurement error, and therefore could be a useful outcome measure in lacunar stroke rehabilitation.

In the present study, we conducted a familiarization test to minimize a potential learning effect. We recommended this for use in clinical practice to achieve similar results. During the test trial, most patients used closer to 15 seconds than 10 seconds to recite the standardized text passage. This may be explained by minor cognitive symptoms, visual problems, vertigo, or dysarthria. The test protocol was adjusted accordingly to the test–retest sessions and all patients completed without problems.

Table 2. *Relative and absolute reliability of the Graded Cycling Test with Talk Test*

	Test 1 (W) Mean ± SD	Test 2 (W) Mean ± SD	Difference ± SD (W)	$ICC_{2.1}$ (95% CI)	SEM (W)	SEM_{95} (W)	SRD (W)
TT+	88.5 ± 37.2	88.8 ± 36.4	.3 ± 15.0	.92[.87-.95]	10.6	20.8	29.4
TT–	114.8 ± 37.0	114 ± 35.6	.8 ± 9.3	.97[.95-.98]	6.6	12.9	18.3

Abbreviations: CI, confidence interval; ICC, interclass correlation coefficient; SD, standard deviation; SEM, standard error of measurement; SRD, smallest real difference; TT+, the subject was able to speak comfortably; TT–, the subject was no longer able to speak comfortably; W, watt.

Relative and Absolute Reliability of the Graded Cycling Test with Talk Test

As illustrated by the slightly larger variability of the results of Talk Test+ (Fig 2, A) compared to the Talk Test– responses (Fig 2, B), the inconsistent use of Talk Test± probably affected the Talk Test+ responses more than the Talk Test– responses, indicating that the patients were not in doubt when they were no longer able to speak comfortably. The reliability and measurement error of Talk Test– were thus superior to Talk Test+, although both responses showed high reliability and low measurement error (Table 2). Therefore, the Talk Test+ is less appropriate as an outcome measure and probably more suited to guide the choice of exercise intensity for exercise prescription, as it has been suggested in cardiac rehabilitation.[10,13,17]

Finding and repeatedly recognizing the exercise intensity at which it was no longer possible to speak comfortably was relatively easy for the patients (Fig 2, B). This is extremely important for clinical practice as well as in research settings as the Talk Test– is the real endpoint of the test.

The absolute reliability of the Graded Cycling Test with Talk Test was calculated to provide clinicians and researchers with an estimate of the true measurable change in watts, with 95% certainty. The SEM was 12.9 W, indicating that patients on group level need to improve above 12.9 W to obtain a real change in workload. On an individual level, SRD was 18.3 W, indicating that a change of 2 steps (30 W) represents a "real" clinical change. The minor measurement error emphasizes that the Talk Test– stage is well suited as an outcome measure for aerobic exercise.

The results in the present study corresponded well with the findings in cardiac patients where Zanettini et al[13] observed a reliability coefficient of .85 for Talk Test– and Nielsen et al[8] found high $ICC_{2.1}$ values for the Graded Cycling Test with Talk Test—i.e., .90 for both Talk Test+ and Talk Test–. In the same study,[8] the absolute reliability was acceptable; SEM_{95}: 18.3 W and SRD: 25.9 W—both results were smaller than 2 steps in the incremental test protocol.

Beta blocking agents are recommended for the treatment of hypertension and cardiac diseases,[24] and it was evident that the Graded Cycling Test with Talk Test was suitable for patients using medication which could potentially affect the heart rate. This is in contrast to other submaximal exercise tests such as the Åstrand Test,[7] which is based on measurement of heart rate in combination with an estimation of maximum heart rate. The fact that the patients affected by beta blocking agents or the presence of atrial fibrillation can use the Graded Cycling Test with Talk Test makes it an appealing alternative for exercise testing of several groups of patients including patients with lacunar stroke.

Because only 1 patient in the present study used beta blocking agents (Table 1), the pulse rates from the 2 test sessions were analyzed. The small difference (3 bpm) between sessions showed that patients experienced breathlessness with the same relative exercise intensity. The reproducibility of the test and the close correlation between the power output (W) and the heart rate at the Talk Test– indicate that the Graded Cycling Test with Talk Test may be used as a valid measure of aerobic exercise capacity also in patients with lacunar stroke.

Limitations

Future research of the Graded Cycling Test with Talk Test in patients with lacunar stroke should address the responsiveness to changes, as responsiveness is an important property of all outcome measures in research as well as in clinical practice. Future studies also need to address the validity of the Graded Cycling Test with Talk Test in patients with stroke as we need solid evidence that the Graded Cycling Test with Talk Test measures submaximal exercise intensity. Further, it would also be important to show that this test is suitable for other subtypes of stroke, as long as they are capable of sitting on a stationary bike.

Another interesting aspect of the Talk Test that warrants further investigation is the potential role of the Talk Test as a guide to the exercise intensity under unsupervised exercise sessions for patients with lacunar stroke. So far, studies in cardiac rehabilitation have indicated that the Talk Test can be used as an intensity guide.[13,25,26]

Conclusion

The "Graded Cycling Test with Talk Test" is feasible in patients with lacunar stroke. The small measurement error and excellent relative reliability indicated that the test can be used as an outcome measure in clinical studies. The Graded Cycling Test with Talk Test is also user-friendly and not time consuming, hence it is suitable in research settings as well as in clinical practice.

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Home-based aerobic exercise in patients with lacunar stroke: design of the HITPALS randomized controlled trial

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Abstract

Background

The effects of physical exercise in patients with lacunar stroke, seem promising in secondary prevention and only few studies have investigated the effect of high-intensity interval training in patients with lacunar stroke. This study will be investigating whether high-intensity interval training improves cardiorespiratory fitness as well as cognitive- and endothelial function and potentially attenuating the risk of recurrent stroke.

Methods

A randomised controlled trial evaluating 12 weeks of home-based, high-intensity interval training compared with usual care. The intervention group will be exercising 15 minutes a day, 5 days a week, for 12 weeks. Outcomes will be evaluated at baseline, three, six and twelve months post-stroke with 'The Graded Cycling Test with Talk Test' as the primary outcome registered as power output in Watts. Additionally, an annually register-based follow-up will be performed for 5 years from date of inclusion with a composite endpoint of cardiovascular disease or death. Secondary outcomes will be: physical activity, endothelial response, mental well-being, cognition, mood, fatigue, stress, and MRI scan.

Discussion

This study is going to show if early initiated home-based high-intensity interval training is feasible and effective in patients with lacunar stroke. A self-chosen aerobic exercise modality allows a realistic implementation of practice, together with greater chance of long-term adherence. A limitation of the study is that recruitment bias cannot be ruled out, as there may be a preferential enrolment of patients who are self-motivated to engage in exercise.

Trial registration number

This study is registered at ClinicalTrials.gov (NCT02731235, registered January 2016).

Keywords

High-intensity interval training, lacunar stroke, risk factors, secondary prevention

Introduction

Lacunar stroke accounts for one in four of all ischemic strokes (1), and it is associated with a three-fold increase in the risk of a new stroke and a high risk of cognitive decline and dementia (2). Similar to other stroke subtypes, the risk of a recurrent stroke is increased by co-factors such as diabetes (2), hypertension, smoking (3), and physical inactivity (2). Recurrent strokes are usually more debilitating, with worse prognosis and outcome, and a higher rate of discharge to long-term care facilities (4). The current secondary prevention of recurrent stroke is antithrombotic, anticoagulant, antihypertensive and cholesterol reducing treatment in addition to non-pharmacological interventions and lifestyle changes. As the risk of recurrent stroke is between 3.7–6.7% within 90 days from stroke (5, 6), secondary prevention including lifestyle modifications should be initiated promptly (7). Physical activity is an important lifestyle modification to many co-morbidities (8). Physical activity with improved cardiorespiratory fitness reduces lipids, blood pressure and weight, thus promoting improved cardiovascular health (9, 10) with reduced morbidity and mortality (11). Regular physical activity may also help minimize the cognitive deficits post stroke (12).

Studies on stroke survivors identifies sedentary behaviour after stroke (13, 14), with activity levels below that of people with chronic diseases of musculoskeletal or cardiovascular origin (15). The cause of the reduced physical activity is not fully understood as many patients with stroke are able to be more physical active but choose not to be (16). This may represent a knowledge gap on exercise recommendations, fear of exercise inducing stroke, or lack of support in daily physical activities (17).

We hypothesize that implementing high-intensity interval training at home (defined as vigorous-intensity physical activity performed at ≥6 Metabolic Equivalent of Task (MET) (18)) within the first three weeks of a lacunar stroke will improve cardiorespiratory fitness, physical activity, cognition, endothelial response, and quality of life. Previous studies have shown that supervised high-intensity interval training in patients with stroke are feasible and effective in the late post-stroke phase (19). Therefore, the aim of this study will be to compare an improvement in cardiorespiratory fitness across a 3-month period of home-based high-intensity interval training compared with an improvement in cardiorespiratory fitness in usual care. Furthermore, we are going to investigate changes in risk profile for a recurrent stroke with long-term follow-up on cardiovascular events.

Methods and analysis

The study will be a parallel, two-arm, randomized controlled trial. In addition to usual care (preventive medication and advice on self-managed life-style changes), the intervention group will be doing home-based high-intensity interval training during the first three months post stroke compared with only usual care. Eligible patients with recent (0-21 days) onset of symptoms of a lacunar stroke will be randomized to intervention or usual care group. Patients will be assessed post-intervention, and at follow-up (6 and 12 months post stroke) (Figure 1). Subsequently, the patients will be followed annually for five years after stroke using patient records, national registries and questionnaires evaluating numbers of vascular events or death. Furthermore, baseline data from this RCT will be constituting a cross-sectional study on self-reported pre-stroke physical activity and post-stroke health profile in patients with lacunar stroke.

Recruitment

All patients will be in-patients recruited consecutively from the stroke unit at Herlev Gentofte University Hospital, Copenhagen from January 1st, 2016 with a target of 100 included patients. Recruited patients for inclusion will be first episode lacunar stroke or patients with recurrent lacunar stroke with clinical symptoms and a corresponding ischemic lesion verified on MRI scan.

Participants

Lacunar stroke is defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST-criteria) (20) where the patients have one of the traditional clinical lacunar syndromes, with relevant brain stem or subcortical hemispheric lesion verified on CT scan or MRI scan. In the acute phase, the lesion has a diameter < 2 cm (21), no cerebral cortical dysfunction, no potential cardiac source for embolism and in case of arterial stenosis, occlusion should be < 50%. During admission patients will be routinely examined with chest x-ray, continuous electrocardiogram (ECG-monitoring) for 48 hours (for heart arrhythmias) and carotid artery stenosis screening (ultrasound). Inclusion criteria will be, symptoms of an acute lacunar stroke, either with corresponding acute lesion on MRI scan, or with a previous lacunar stroke on MRI scan (amendment 1, June 2016), age > 18 years, able to speak and read Danish, and be able to give informed consent. Exclusion criteria will be prior large artery stroke, symptoms or co-morbidities in the musculoskeletal system preventing exercise on a stationary bike, uncontrolled hypertension or diabetes, dyspnoea caused

by heart or pulmonary disease, atrial fibrillation, carotid artery stenosis (occlusion > 50 %), aphasia or cognitive dysfunction interfering with the Talk Test.

Screening process and enrolment

Eligible patients will be identified by daily screening of medical records and they will be provided with written and oral information about the study. Informed consent will be obtained by the study coordinator and includes consent to collect and store biological specimens. After completion of the baseline assessment, the patients will be assigned to either intervention or control group. Personal information about the patients will be collected, maintained and stored to protect confidentiality before, during and after the trial. Only the study coordinator and physicians involved in the study will have access to the final trial dataset.

Randomization/blinding

The patients will be randomized consecutively into two groups: exercise intervention and usual care or usual care only, based on equal allocation with randomly varying block size. A computer-generated block-randomization (8 blocks of 10, mixed with 5 blocks of 4) will be administrated by a research assistant not involved in the study, and unaware of patient assignment. Outcome assessor, data analysts and, study coordinator will be blinded to the randomization process. Sealed opaque envelopes made by the research assistant will be stored and administrated by other personnel not involved in the study.

Outcome assessments

All outcome measures, except MRI scan, will be obtained at baseline (0-21 days post stroke), post-intervention, 6 and 12 months post stroke and subsequently registry-based outcomes will be obtained yearly (Table 1). The study will be reporting at the prespecified time-points with the same primary outcome (Power output from the Graded Cycling Test with Talk Test (GCT-TT)). The first reported time point (after baseline) is the post-intervention assessment, i.e. after 3 months, where we aim to investigate the acute effect of the intervention (home-based high-intensity interval training).

The subsequent follow-up assessments at 6 months and at 12 months will be reported together after the 12 months assessment to explore whether the intervention group have made sustainable

lifestyle changes and kept the achieved exercise level post-intervention assessment. At the 12 months follow-up the explorative analysis on the MRI outcome changes will be done.

The primary outcome, is the change in power output registered in Watts (W) from the GCT-TT. It will be performed by assessors, not involved in the study and not performed in immediate association with the intervention. Prior to the study the assessors will be introduced, trained and calibrated in performing the GCT-TT (3 tests in healthy adults and 3 tests in patients with minor stroke) by the study coordinator.

Data from the secondary outcomes will be collected by the study coordinator with prior training in administering questionnaires and assessment tools. Data containing personal information will be collected, anonymized and stored to protect confidentiality. Data access will be limited to the study coordinator and physician involved in the study.

Primary outcome

The power output registered in Watts (W) from the GCT-TT will be the primary outcome measure. The Talk Test (TT) in itself is a simple and valid estimate to evaluate submaximal exercise intensity (22-29) and it is responsive to estimate changes in aerobic capacity following blood donation and aerobic training (25). The Talk Test has previously been used in combination with various incremental exercise test protocols on treadmill (24, 25, 27-32) or a stationary bicycle (22, 26, 32). We will use TT with the GCT protocol, which is a frequently used protocol in Denmark, where the general population are accustomed to cycling. The GCT is performed on a stationary bicycle (Monark 928E-G3, Vansbro, Sweden) using a ramp protocol with a 15 Watt increase each minute (33). During the last 10-15 seconds of each minute, the patients recite a standardized text passage, followed by the question: "are you able to speak comfortably?". The patients can answer "yes", "unsure" or "no", and the test stops when the patient answers "no" (not able to speak comfortably). This point, identifies the highest possible exercise intensity where the patient can speak comfortably without feeling disturbed by increased breathing. A detailed test-protocol has previously been described (34).

The GCT-TT can be performed independently of the ability to assess the maximal heart rate (e.g. in case of atrial fibrillation or beta-blocker). Furthermore, it is easy and time effective to use, and it does not require expensive equipment. Also, the test is assessor-independent, as it is the patient who identifies the intensity level where he/she cannot speak comfortably. These qualities of the GCT-TT make it an attractive outcome measure in various rehabilitation settings. The GCT-TT

has shown good reliability and minor measurement error in both patients with ischemic heart disease (35) and in patients with lacunar stroke (36). The standard error of measurement with 95 % certainty (SEM_{95}) in patients with lacunar stroke is: 12.9 Watt. Thus, a change of ≥12.9 W reflects a real change in power output beyond measurement error in a group of patients with lacunar stroke. For an individual patient with lacunar stroke, the smallest real difference (SRD) is 18.3 Watt, indicating that a change of two steps in the incremental test protocol (30 Watt) represents a real clinical change.

Long-term follow-up (5 years)

Patients will be followed 5-years post-stroke using patient journal, registers (The Danish National Patient Registry and The Danish Stroke Registry) and questionnaires to evaluate number of incidence of cerebrovascular events (recurrent stroke) or death.

Secondary outcomes

Choices of secondary outcomes are based on an interest to monitor potential improvement in symptoms of stroke and risk factors for recurrent stroke. We also considered whether the questionnaire was validated in a stroke population and was available in Danish, and the total time spend on each outcome.

Endothelial function

Endothelial dysfunction is a known risk factor for cardiovascular diseases (37), hypertension (38), hypercholesterolemia (38), and stroke (39).

Endothelial function is measured by a non-invasive method determining the peripheral arterial tonometry (PAT) by EndoPAT2000 (Itamar Medical Ltd., Caesarea, Israel). The PAT is measured by plastic probes that impart a uniform pressure to the distal two third of the index finger. The endothelial function estimates the changes in pulse wave amplitude (PWA) and is registered as the reactive hyperemia index (RHI). RHI is the post- to pre-occlusion signal ratio in the occluded arm compared to the same ratio in the control arm and corrected for baseline vascular tone of the occluded arm. A detailed test procedure is previously described (40). A lower RHI-value is associated with impaired endothelial function (41). A RHI-value >1.67 is recommended as cut-off for normal endothelial function (abnormal function is ≤1.67), recommended by the EndoPAT2000-user manual. Furthermore, arterial stiffness is estimated using the augmentation

index (AI) and based on computerized averaging and analysis of multiple pulse waveforms registered during baseline measurement on the occluded arm. AI register change in peak systolic pulse wave after baseline occlusion (%). Also, the heart rate-corrected augmentation index (AI@75) is measured at the heart rate of 75 beats per minute. A previous study investigating validation of repeated measurement of endothelial function in patients with acute stroke found good day-to-day reliability (40).

To reduce potential day-to-day variability, the assessment will be carried out in the morning and the patients will be asked to refrain from consuming any food or beverages after midnight. Assessment will be performed in an undisturbed, dark room with a room temperature of 21-24^{o} C. Before assessment, the patient will relax in supine position for 25 minutes to reach cardiovascular steady state.

Physical Activity

Physical inactivity is one of the major risk factors for stroke why it is relevant to explore (42). Physical activity will be measured using a self-reported questionnaire; physical activity scale version 2.1 (PAS2) (43) and objectively with accelerometers worn by the patient for a week at baseline, post-intervention, and at 6 and 12 months, respectively.

PAS2 measures physical activity as daily hours and minutes of sleep, sitting, standing or walking, and heavy physical work, transportation to and from work, as well as TV-watching or reading. In addition, PAS2 measures weekly hours and minutes of light-intensity physical activity, moderate intensity activity, and vigorous-intensity activity (43). Each of these domains correspond to a specific level of MET-intensity (The Metabolic Equivalent of Task) (44), where 1 MET is the rate of energy expenditure while sitting at rest and corresponds to an oxygen uptake of 3.5 ml/kg of body weight/minute. Moderate-intensity activity refers to the physical activity performed at 3.0-5.9 METs and vigorous-intensity activity correspond to >6 METs (18). The total measurement of METs allows for indirect estimation of total physical activity during 24-hours. The construct validity of the physical activity scale has been validated in 342 Danish men and women aged 35-66 years (43).

Objective assessment of activity by accelerometer

Objective assessment of physical activity will be measured with a water resistant and wireless three-axis accelerometer, AX3 (Axivity, York, UK), recording with a frequency of 25 Hz. It will

be fixed with double sided adhesive tape (VIP Tape, Skinlock International, Charleroi, Belgium), and sealed with a water-resistant patch (Fixomull® transparent, BSN medical Inc., Hamburg, Germany) anteriorly on the thigh. The position of the AX3 will be right medial thigh; midway between the hip and knee joint, orientated with the x-axis pointing downward, y-axis horizontally to the left, and z-axis horizontally forward. The accelerometer will be initialized for recording and data downloaded using manufacturer´s software (Open Movement v.1.0.0.28). Data from the accelerometer will be analysed using Acti4, a custom made script in MATLAB (version R2013a) including a previously described algorithm to identify everyday physical activity types such as walking, running, cycling, climbing stairs, standing and sitting (45). Activity patterns will be recorded for 8 days and 7 nights, including data from both weekdays and weekends. The AX3 is validated in healthy subjects with a high specificity and sensitivity to differentiate between the above-mentioned activities (45, 46). The monitor device will be set during patient assessments at the hospital and returned by mail using pre-paid envelopes. Furthermore, all patients will keep an exercise diary reporting type, amount (in minutes) and intensity of activity daily, for 12 weeks.

Well-being

To evaluate well-being, we will be using the WHO-5 Well-Being Index. It is a short, self-rated questionnaire evaluating mental well-being (47). It has adequate validity both as a screening tool for depression and as an outcome measure in clinical studies (47). The WHO-5 Well-Being Index includes five positive statements on mental well-being over the last two weeks, with respondent answers distributed on a 6-point Likert-scale. The raw-score is calculated by summation and ranges from 0-25 (the higher the score the better mental well-being) and is often expressed as percentage of the maximal score (48). To monitor changes in mental well-being, a relative (percentage) score change of 10% is used to indicate significant change (49). The cut-off score indicating risk of depression or long-term stress is set to 50 points (50) while the average score for the Danish population is 69 points (48).

Cognition

The Montreal Cognitive Assessment (MoCA) is a brief screening tool designed to identify mild cognitive impairments. It assesses different cognitive domains: attention, concentration, executive functions, memory, language, visuospatial ability, conceptual thinking, calculations and

orientation. The total score is 30 points and a score ≥26 is considered as normal (51). The MoCA is valid and reliable in patients with lacunar stroke and white matter lesions (52).

Depression

The Major Depression Inventory (MDI) is a self-reported questionnaire for diagnosing and assessing depression (53). The questionnaire includes twelve questions on how the patient has been feeling over the past two weeks. The response is given on a 6-point Likert-scale, where 0 corresponds to: ”At no time” and 5 corresponds to “All the time”. The maximum score is 50 points and the higher score the more severe the depression (53). A score >20 points indicates mild depression, while a score >15 points indicates incipient depression (54).

Fatigue

Multidimensional Fatigue Inventory (MFI-20) is a 20-item self-report instrument evaluating five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity (55). Each dimension is covered by four questions and the responder indicates on a 5-point Likert-scale, to what extent the statement applies to him/her. Each dimension of fatigue is calculated on a score from 4-20, with higher scores representing increased fatigue (55, 56). We use the domain of general fatigue as a measure of overall fatigue as proposed in the original development of the scale (55).

Chronic Stress

Chronic stress will be measured using an algometer (Ull-Meter®), an objective instrument measuring the pain threshold on the sternum, called pressure pain sensitivity (PPS) (57, 58). The algometer is the size of a whiteboard marker and is easy to use. The patient will be in a supine position, and for 5 seconds the Ull-Meter will be gradually pushed against the area identified as the most sensitive point of the sternum. When the patient experiences discomfort, the pressure is stopped and the PPS is read on a scale from 30-100, with a cut-off point ≥60, correlating with markers of a stress syndrome (59). The result is blinded from the observer until the measurement has finished (57, 58). In both healthy people and patients with chronic disease such as ischemic heart disease, PPS is associated with several elements of the chronic stress syndrome: depression score, quality of life scores, and numbers of stress reactions (57-59). Stress intervention studies aiming at reducing PPS have demonstrated clinically relevant reduction in several risk factors for

ischemic heart disease and in healthy control subjects (60). Furthermore, in a previous study on patients with ischemic heart disease, stress-reducing treatment aiming at reducing PPS demonstrated a concomitant decline in major depression inventory (MDI) and an increase in mental well-being (WHO-5 Well-Being Index) (61).

Blood pressure

The blood pressure (systolic and diastolic pressure) will be measured following an overnight fast. With the patient in a supine position and after 5 minutes of rest, blood pressure will be measured with an automatic blood pressure monitor (Microlife® BP A100/ Microlife® BP A3L Comfort, Widnau, Switzerland).

Blood samples

To evaluate possible endothelial dysfunction, inflammation and risk of cardiovascular event we hypothesize a reduction in endothelial biomarkers (Vascular endothelial growth factor (VEGF), vascular cell adhesion molecule 1 (VCAM-1), intercellular Adhesion Molecule 1 (ICAM-1), E-selectin), inflammatory biomarkers (Interleukin-6 (IL-6), tumour necrosis factor (TNF), high sensitivity C-reactive protein (hsCRP); lipoprotein(a) (LIPA)) and in cardiovascular biomarkers (pro-Adrenomedullin, pro-atrial natriuretic peptide and Copeptin); glucose metabolism. Furthermore, a battery of routine analyses will be performed on the day of examination (Table 2). The inflammatory biomarkers and endothelial biomarkers will be analysed according to the manufacturer´s instructions, using commercially available kits from Mesoscale, Rockville, USA. (V-PLEX Plus human: IL-6 kit, TNF kit, ICAM-1 kit, VCAM-1 kit, VEGF kit, and E-selectin kit). The cardiovascular biomarkers will be analysed according to the manufacturer´s instructions using commercially available kits and software from BRAHMS GmbH, Hennigsdorf, Germany. (KRYPTOR compact PLUS human: Pro-ADM kit, Pro-ANP kit, and copeptin kit). All blood samples will be collected during fasting state and stored at -80^0 C until analysis.

Body Mass Index

Information on body weight and Body Mass Index (BMI) will be acquired with a body composition monitor (OMRON HBF-500-E; Kyoto, Japan). The height will be measured in centimetres and entered in the body composition monitor together with sex and age.

Magnetic Resonance Imaging

Magnetic resonance Imaging (MRI) will be obtained at baseline and at 12 months post stroke at Herlev Gentofte University Hospital, Department of Radiology. Data is blinded for patient participation and stored in a secure departmental network system. The scanning protocol will consist of an initial set of anatomical scans (T1W, T2W, inversion recovery and FLAIR), that serve as basis for radiological assessment. Furthermore, a diffusion tensor imaging (DTI) sequence is acquired followed by an arterial spin labelling sequence (ASL) to quantify tissue perfusion, two 3D T1W sequences at different flip angles (FA 7 and FA 20) to estimate the T1 time of the tissue and finally, a high spatial resolution dynamic contrast-enhanced sequence (DCE) will be used to gauge blood-brain barrier permeability. For the DCE sequence a single dose (0.2 ml/kg) of gadolinium (DOTAREM, Guerbet, France) will be injected at the rate of 3ml/sec. All scans will be performed on a 3T clinical system (Ingenia, Philips Healthcare, Best, The Netherlands) using a 32 element headcoil. The total scanning time per patient is 50 minutes at each time-point (Table 3).

Other data collection

The following data will be retrieved from the patient record or the patient: co-morbidity, symptoms, medication, smoking- and drinking habits, educational level and occupation.

Intervention

Physical activity is one of the modifiable risk factors for stroke (42) and should be initiated early after stroke. Many patients with stroke may not be familiar with regular physical exercise hence the intervention must be simple, motivating, not time-consuming, realistic and easy to perform during daily living routines. To describe the intervention, Consensus on Exercise Reporting Template (CERT) has been used (62).

In addition to usual care, the intervention group will perform unsupervised high-intensity interval training at home, 15 minutes a day, five days a week for twelve weeks. High-intensity interval training is performed in short bouts of rather high, but not maximal-intensity aerobic exercise alternating with short periods of low intensity exercise (63). The 15 minutes of high-intensity interval training corresponds to the WHO global recommendations on physical activity for health. WHO recommend at least 75 minutes of aerobic physical activity at vigorous-intensity throughout

a five-day week. The exercise modality will be tailored under the condition that it is aerobic, and the intensity will reach the level where the patient is not able to speak comfortably.

All patients will attend a motivational talk with the study coordinator at baseline with the purpose to encourage lifestyle behavioural changes. The patients will also be introduced to an exercise catalogue, presenting various modes of aerobic exercise. The catalogue will consist of: brisk walking/Nordic walking, stair stepping, knee lifting, outdoor cycling/cycling on a stationary bike, and running – all exercise modalities aim to elicit an increase in heart rate.

To ensure an easy accessible exercise modality, all patients will be offered to borrow a stationary bicycle (Kilberry® Magnetic Bike JC-950, Proteus Sports Inc., Linkou Township, Taiwan) to use at home. The bike monitors: time (minutes), distance (kilometre), energy expenditure (calories), speed (kilometres per hour), resistance (level 1-9), heart rate (pulse) and cadence (rounds per minute), all of which are used for motivation purpose. Furthermore, all patients will be provided with a pocket sized, laminated standardised text passage (cue card), which they will use to find the exercise intensity.

Duration of intervals and mode of recovery vary between different study-protocols (64) thus, we have chosen an easy, realistic and clinical implementable exercise program. The aerobic exercise will be performed in intervals. Two minutes of warm-up (at self-chosen level) followed by three minutes of high-intensity interval training at the intensity where the patient cannot speak comfortably any longer (corresponding to the answer "No" in the Talk Test). This will be followed by two minutes of moderate intensity, followed by three minutes of high intensity and so forth for 15 minutes, each session. The feasibility of each exercise modality on how to achieve out-of-breath level (e.g. TT) was tested in four healthy individuals prior to study planning. Before patients start exercising the study coordinator will visit the patients at home to introduce the exercise program, including an introduction to the Talk Test (how to reach the right exercise intensity and how to progress the exercise program). The Talk Test will determinate the starting level of the intervention and the patients will progress the intensity of the exercise modality (e.g. when using the bicycle by increasing the work load or the cadence) as they improve throughout the exercise program. At every session patients will be encouraged to reach an exercise-intensity level where they can no longer speak comfortably. For further motivation and control of completion of work-out, the patients will be contacted by phone, text message or e-mail on a weekly basis to ensure compliance. The weekly call(s) will also be an opportunity to identify equipment malfunction or adverse events. Adverse events will be documented in the case report form (CRF). All exercise

sessions will be tracked by an individual exercise diary to ensure adherence. Adherence to the study in general is encouraged by highlighting the importance of both groups in producing valid study results.

Control group

The control group will receive usual care, consisting of individually adapted preventive medication and advice on lifestyle changes. Furthermore, they will be asked to resume their usual level of physical activity and to track their activity in an individual exercise diary, documenting type, time, and intensity of exercise.

Both the usual care group and the intervention group will be offered a control visit with a nurse at the preventive outpatient clinic (Herlev Gentofte University Hospital) within 2 months from stroke onset. The purpose of the visit is to evaluate blood pressure and cholesterol level and to ensure appropriate medication. Furthermore, the purpose is to provide advice on lifestyle changes regarding; food, smoking and alcohol intake.

Adverse events/Discontinuing

Adverse events will be monitored and registered during the study. Discontinuation will be considered if a patient is either unexpectedly readmitted to the hospital or emergency department for a disease other than stroke, or if they experience severe symptoms such as musculoskeletal pain, fracture or cardiac symptoms of any kind.

Statistical analyses

Sample size and statistical analyses

A sample size calculation based on the primary outcome (Graded Cycling Test with Talk Test) was conducted with a standard deviation (SD) of 37 Watt and a meaningful difference of 23 Watt. 84 patients (42 in each group) are needed with a power of 80% and a two-tailed α of 0.05. With dropouts taken into account (15%), we will aim to include 100 patients in total.

Data, from patients with complete outcome data, will be analysed according to the group to which they were randomised, independent of patient compliance. All available data for each patient will be included in the analysis, also if the patient does not have all observations. Missing data will not be imputed. The estimated treatment effects will be calculated by the constrained longitudinal data analysis (cLDA) which will give unbiased result under missing at random. In case of one patient is missing all observations post baseline, the patient will be excluded in the analysis. An

explorative analysis will be conducted to test for interaction effects on the following parameters; sex, age, family status, and education. The rationale for performing this analysis is that no prior studies have explored the effect of these parameters on exercise efficacy in lacunar stroke. A general linear mixed effect model with baseline constrains will be used for both primary and secondary outcomes using constrained longitudinal data analysis (cLDA) (65). No other independent variables will be included in the analysis. The effect-size will be calculated as the visit/treatment interaction at the specified visit and given as model estimates of mean difference with 95% confidence interval (CI). Changes over time within each assessment day on all relevant outcomes will be performed with linear mixed effect model and patients who do not show up at the assessment visits will be counted as missing at that specific assessment point.

The 5-year outcomes, survival and cerebrovascular events, will be analysed using time-to-events method. The Kaplan-Meier method will be used for descriptive survival statistics and drawing survival curves, and the Cox proportional hazard model will be used for analysing confounders of survival and cardiovascular events. The long-term analysis will be explorative as we do not expect it to have adequate power as the study is not powered to detect differences on long-term outcome between treatment groups. Data from all included patients in the baseline assessment will be used, except from the patients lost to follow-up.

The analysis of the MRI scans will be performed with statistical parametric mapping (SPM) with a paired design.

Before analysis, all variables will be controlled for normal distribution, and transformed if needed. Non-parametric testing will be used if data diverge from normal distribution after transformation. All tests will be two-sided and p-values < 0.05 will be considered significant. Data will be analysed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics 22 (Armonk, NY, USA) or a similar software. Statistical planning is conducted in cooperation with a biostatistician.

Ethics approval and consent to participate

The study has been approved by The Danish Data Protection Agency (ID: HGH-2015-021) and adhere to the Danish low of data protection. Furthermore, the study has been approved by the Research Ethics Committee in the Capital Region of Denmark (H-15012371) according to the Declaration of Helsinki of 1964, as revised in 2008. The study is registered at ClinicalTrials.gov (NCT02731235, registered Jan. 2016) and the reporting adheres to the SPIRIT 2013 statement (66). All participants will provide written informed consent before enrolment. Results of this study

will be published in peer-reviewed international journals and they will be presented at international and national conferences.

Protocol H-15012371 (version 4.0, June 2016) amendment 1 has been modified to allow an extended inclusion period from 0-21 days (previously 0-7 days). In addition, inclusion of patients with recurrent lacunar stroke, with clinical symptoms and a corresponding ischemic lesion on MRI will be allowed. Amendment 2 (version 5.0, June 2017) will be allowing inclusion from two other stroke units in the Capital Region of Copenhagen due to low recruitment rate. The article describes protocol version 5.0 from June 6th. 2017.

Discussion

The aim of this study will be to report results on an early aerobic intervention carried out in the home environment of the patients. Firstly, this study will investigate whether it is possible to engage patients in physical exercise early after stroke. Secondly, it will investigate whether it is feasible and safe for patients with lacunar stroke to do high-intensity interval training in their home environment and to explore their adherence to exercise on a regular basis for twelve weeks. Thirdly, we will monitor the long-term effects of the intervention on cerebrovascular events and death (5 year).

If the intervention turns out to be feasible and effective, this study will potentially contribute to establishing recommendations on exercise programs and guidelines for patients with lacunar stroke. It will also be interesting to explore whether there is a difference of having encouraging phone calls on a weekly basis (intervention group) or the physical assessments in itself at the post-intervention assessment (control group) are sufficient. Furthermore, it will be interesting to explore, at six and twelve-months follow-up, how many patients have kept doing exercise on regular basis. This will provide us with information on how easy or difficult it is to integrate physical activity as a routine in daily living after lacunar stroke.

A strength of this study will be that patients can choose their preferred modality of aerobic exercise, as long as they exercise with an intensity where they are unable to speak comfortably. With a self-chosen exercise modality, the chances of long-term adherence will potentially be higher. The home-based intervention will allow training to occur at times which are suitable for the patient, just as it eliminates limitations associated with transport to training facilities. As all patients will be assessed post-intervention using GCT-TT on a stationary bicycle, the free choice of exercise modality might be a potential bias. It has been suggested that submaximal exercise

thresholds such as ventilatory threshold (VT) occur at a relatively lower exercise intensity during incremental exercise tests using unfamiliar exercise modalities – i.e. runners reach VT at a lower percentage of VO_{2max} during cycling than running (67). Consequently, it could be expected that patients who choose to exercise on stationary bicycles might perform better on the GCT-TT compared with patients who choose to run.

To ensure a safe exercise intensity post stroke a continuous ECG-recording for 48 hours will be performed during hospitalization. Furthermore, the patients will be completing their first aerobic exercise test at the hospital in a safe environment together with an experienced physiotherapist. Both actions should help making the patients feel safe when exercising at home. Another strength is the relatively large sample size used which will allow the finding of the study to be generalized to other patients suffering from a lacunar stroke.

A limitation of the study will be the monitoring of physical activity for one week only rather than the entire exercise period. Another limitation is not being able to monitor the exercise intensity with heart rate monitors. A field-test prior to study planning showed that when recording heart rate with ECG-electrodes for more than 3-5 days, the risk of developing eczema on the chest was high, rendering poor quality data. The use of commercially available heart rate monitors will be a challenge as the study population are elderly with potential cognitive deficits. Secondly, the current commercially available heart rate monitors have a limited battery life and a limited memory capacity. Therefore, we anticipate that the data quality will be too low if patients are unable to comply with correct use of equipment that needs frequent recharging. Instead, patients will record the amount of exercise in a diary. A possible bias may be that only patients intended to engage in exercise will choose to participate in the study. If this influences the activity of the control group, it could diminish the difference in outcome measures between the groups. This study will contribute information about the use of early high-intensity interval training in patients with lacunar stroke. Furthermore, we test the hypothesis that exercise can increase cardiorespiratory fitness and endothelial function and as a result, slow progression of vascular diseases and potentially prevent recurrent stroke.

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Authors´ contributions

All the authors contributed to the study conception and design. RSK and CK contributed to obtain funding. RSK, AV and CK drafted the manuscript. All authors reviewed the manuscript, provided comments and revisions as well as read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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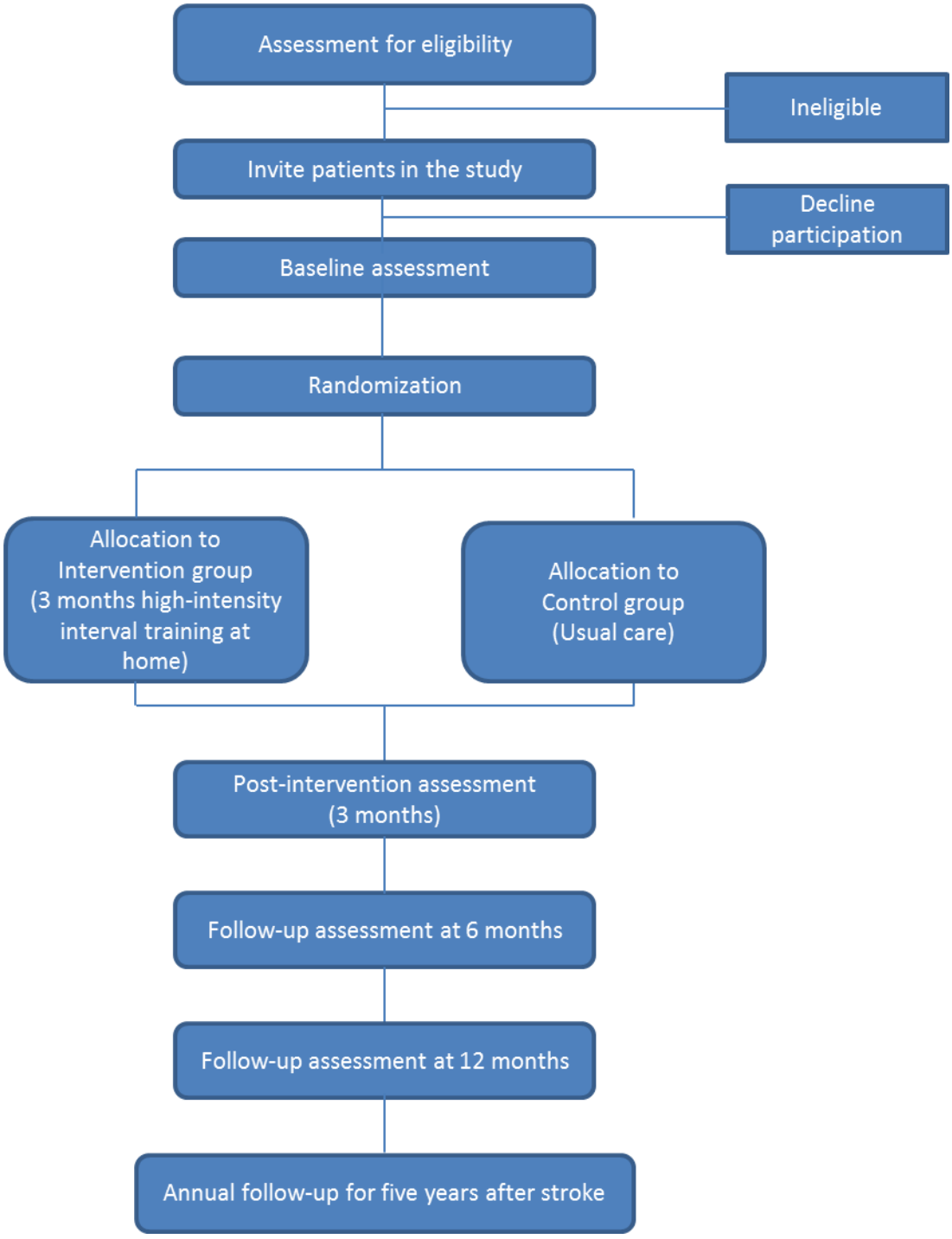

Figure 1. HITPALS-trial, work flowchart

Outcomes	Abbreviation/ device	Function
Primary outcome		
Power output in Watts from the Graded Cycling Test with Talk Test	GCT with TT	Submaximal aerobic exercise test
Secondary outcomes		
Endothelial response	EndoPAT2000	Endothelial function
Physical Activity Scale	PAS2	Self-rated physical activity
Axivity	AX3	Accelerometer monitoring physical activity
Mental well-being	WHO-5 Well-Being Index	Self-reported mental well-being
Montreal Cognitive Assessment	MoCA	Assessment of cognitive function
Major Depression Inventory	MDI	Self-reported depression symptoms
Multidimensional Fatigue Inventory	MFI-20	Self-reported fatigue symptoms
Chronic stress	Ull-Meter	Objective measurement of the body and mind's state of stress
Vascular risk factors:		
Blood pressure (resting)	BP	Systolic and diastolic blood pressure
Blood samples	BS	Measure of total cholesterol/ high-density lipoprotein ratio, cardiovascular biomarkers, inflammatory biomarkers and endothelial biomarkers
Body Mass Index	BMI	Quantify the amount of tissue mass (muscle and fat)
MRI scan	MRI	Changes in brain structure after 12 months (regarding infarcts, white matter lesions, micro bleeds)

Table 1: Outcome assessments

Category	Name of blood sample	Units
Hematology	Hemoglobin	mmol/L
	Leucocytes	$x10^9$/L
	Thrombocytes	$x10^9$/L
Electrolytes	P-Glucose	mmol/L
	P-Creatinine	µmol/L
	P-Potassium	mmol/L
	P-Sodium	mmol/L
Proteins	P-Albumin	g/L
	P-Reactive Protein (CRP)	mg/L
	P-Reactive Protein (HSCRP)	mg/L
Enzymes	P-Creatine	U/L
	P-Alanintransaminase (ALAT)	U/L
	P-Aspartattransaminase (ASAT)	U/L
Hemostasis	P-Coagulation factors (APTT)	S
	P-Coagulation factors (INR)	S
Endocrinology	Glucose (HbA1c)	mmol/L
	P-Thyrotropin (TSH)	$X10^{-3}$IU/L
Lipids	P-Cholesterol	mmol/L
	P-cholesterol (LDL)	mmol/L
	P-cholesterol (HDL)	mmol/L
	P-Triglyceride	mmol/L

Table 2: List of routine blood samples
P: plasma, U/L: units/litre, S: Seconds

Sequence order	MRI-sequence	Purpose	MRI parameters
1	T1W 3D gradient seq. (GRE). (sagittal – S)	First seq. merely for planning purposes	TR/TE(ms) 25/1.68 Voxel(mm) 1 x 1 x 6
2	Inversion recovery with 3D GRE acquisition (S)		TR/TE 6.9/1.68 Voxel 1.1 x 1.1 x 1.1
3	T2W spin echo (SE) seq. (axial – Ax)		TR/TE 3000/80 Voxel 0.5 x 0.5 x 4
4	T1W GRE (Ax)		TR/TE 288/4.6 Voxel 0.5 x 0.5 x 4
5	Fluid Attenuated Inversion Recovery (FLAIR)	For delineation of white matter lesions, hyperintensities corresponding to leukoaraiosis (Ax)	TR/TE 11000/2800 Voxel 0.5 x 0.5 x 4
6	Diffusion Tensor Imaging seq. (Ax)	For 3D indication of neural bundles and DWI assistance in the radiological assessment	TR/TE 11000/2800 Voxel 0.5 x 0.5 x 4 b=0,1000, 32 directs
7	Pseudo-continuous Arterial Spin Labelling (PCASL) (Ax)	For the assessment of tissue perfusion (resting-state CBF)	TR/TE 4040/17 Voxel 2.75 x 2.75 x 5 Label distance 90mm, post delay 1600ms
8	T1W 3D GRE with flip angle (FA) 7 (Ax)	Used to give a rough estimate of the tissue T1 time, which is a parameter in the perfusion	TR/TE 25/1.88 Voxel 0.75 x 0.75 x 4
9	T1W 3D GRE with FA 20 (Ax)	model (Patlak) applied to the DCE data	TR/TE 25/1.92 Voxel 0.75 x 0.75 x 4
10	DCE	To gauge blood-brain barrier permeability. A single dose (0.2 ml/kg) of gadoterate meglumine is injected at the rate of 3ml/sec	TR/TE 25/2.2 Voxel 0.75 x 0.75 x 4 Dyn. scan time 55.7 s No. of dyn. 24

Table 3: Order and type of MRI-sequences

Self-reported physical activity and health profile in patients with lacunar stroke

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Abstract

Physical inactivity is a major modifiable risk factor for stroke. The aim was to explore if stroke patients admitted with lacunar stroke adhere to the international recommendations on physical activity pre-stroke (≥150 minutes of moderate-intensity activity, or ≥75 minutes of vigorous-intensity activity, or an equivalent combination). Further, to assess association between pre-stroke physical activity and stroke risk factors.

Methods

A cross-sectional study, including patients with lacunar stroke according to the TOAST-criteria. Data collected included pre-stroke physical activity using the self-reported Physical Activity Scale (PAS2). Cardiorespiratory fitness was estimated as the power output from the Graded Cycling Test with Talk Test (GCT-TT) and health profile variables including age, sex, education, pre-existing diabetes, hypertension, BMI, and lipids were assessed.

Results

We included 19 women and 52 men (mean age 64 years). Overall, 79% of the recruited patients adhered to the physical activity recommendations pre-stroke but only 35% did vigorous-intensity activity. GCT-TT power output correlated with sex where men reached a higher power output than women. Pre-stroke physical activity correlated with history of hypertension but did not correlate with GCT-TT power output.

Conclusion

A high proportion of our lacunar stroke patients reported to adhere to the recommendations on physical activity pre-stroke however, only one third engaged in vigorous-intensity activity. Higher intensity of activity may be warranted to affect stroke risk in patients with lacunar stroke and may also be relevant to individuals with one or more risk factors of cerebrovascular disease.

Keywords

health profile post-stroke, lacunar stroke, physical activity, risk factors for stroke, secondary stroke prevention

BACKGROUND

Physical inactivity is one of the most important modifiable risk factors to prevent lifestyle-associated diseases such as stroke (1). The American Heart Association and the World Health Organization (2) recommend a weekly minimum of 150 minutes of moderate-intensity activity, 75 minutes of vigorous-intensity activity, or an equivalent combination of the two. This recommendation applies to all individuals aged 65 years or older (2) and to individuals aged 50–64 years with chronic conditions or functional limitations affecting ambulation or fitness (3).

The literature highlights associations between a high level of physical activity in healthy individuals and reduced risk of stroke (4). Whether this also applies to risk of recurrent stroke in patients with a well-known cardiovascular event has not yet been fully established (5). Given that both physical inactivity (6) and low cardiorespiratory fitness (7) are risk factors for stroke, and that increasing age negatively affects cardiorespiratory fitness (8), it is likely that physical activity prior to stroke was already at a low level.

We hypothesized that patients diagnosed with lacunar stroke generally did not adhere to the recommendations on physical activity pre-stroke and that this would likely impact their cardiorespiratory fitness as well as other known risk factors for stroke. To evaluate this, we investigated self-reported pre-stroke physical activity and general health profile, including cardiorespiratory fitness, BMI, blood pressure, lipids and smoking and drinking habits in patients recently diagnosed with lacunar stroke.

METHODS

Design

We analysed baseline data from a randomized controlled trial (The effect of aerobic exercise in patients with lacunar stroke [HITPALS study]) investigating home-based high-intensity training in patients with lacunar stroke. This study was approved by The Danish Data Protection Agency (ID: HGH-2015-021) and the Research Ethics Committee in the Capital Region of Denmark (H-15012371). Eligible patients provided written informed consent before enrolment and the study was registered at ClinicalTrials.gov (NCT02731235, registered January 2016) and reporting adhered to the STROBE statement (9).

Setting

Following stroke diagnosis and acute treatment, patients were enrolled consecutively from stroke units at hospitals in the Capital Region of Copenhagen, Denmark: Herlev Gentofte Hospital, Rigshospitalet Glostrup, and Nordsjaellands Hospital, recruitment period from January 2016 to January 2018. All assessments were carried out at Herlev Gentofte Hospital.

Participants

Patients admitted with a first-time or a recurrent event of a lacunar stroke caused by small artery occlusion according to the Trial of Org 10172 in Acute Stroke Treatment [TOAST] criteria (10) were included. Patients were enrolled after clinical and imaging-based verification of diagnosis by a neurologist. Inclusion criteria: age 18 years or older, ability to speak, read, and understand Danish. Patients were excluded if they had previous large artery stroke, atrial fibrillation, aphasia, dementia, uncontrolled hypertension or diabetes, cardiac or lung disease, carotid artery stenosis >50 %, symptoms or comorbidities that did not allow aerobic exercise on a stationary bicycle.

Procedure

Diagnostic magnetic resonance imaging (MRI) was acquired on a 1.5T clinical system (Achieva, Philips Healthcare, Best, The Netherlands) using diffusion weighted imaging (DWI), apparent diffusion coefficient value (ADC), Fluid Attenuated Inversion Recovery (FLAIR) and T2*-weighted image.

Medical records were screened daily by the study coordinator for eligible patients. From enrolment to first trial visit, eligible patients completed a self-report questionnaire (Physical Activity Scale version 2.1 [PAS2]) at home describing their average weekly physical activity behaviour two weeks prior to hospital admission. The first trial visit took place 12±7 days post-stroke hospital admission with assessment of vascular risk factors (biomarkers, blood pressure, body mass index [BMI]) and cardiorespiratory fitness. All assessments were performed by the study coordinator except evaluation of cardiorespiratory fitness, which was carried out by a specially trained physiotherapist.

Variables

Pre-stroke physical activity

We evaluated pre-stroke physical activity using PAS2, in which patients estimated time spent on various activities. The PAS2 comprises nine questions in total. Six questions address the time spent daily on each of the following activities: sleep, sitting down at work, standing/walking at work, heavy physical work during working hours, active commuting to/from work, and sedentary behaviour. The remaining three questions focus on time spent weekly on light-intensity, moderate-intensity, and vigorous-intensity activity during leisure time (11).

Each activity corresponds to a specific MET (metabolic equivalent of task) intensity according to the compendium of physical activity (12). Physical activity was estimated as a total 24-hour MET score. The performed daily activities were divided into one of four categories: sleep, sedentary behaviour, light activity, and moderate/vigorous activity. Sleep corresponded to 0.9 MET. Television viewing, reading, and sitting down during working hours were categorized as sedentary behaviour (1–1.5 MET). Standing/walking at work, and light leisure-time physical activity were categorized as light activity (2–3 MET). Active commuting to/from work, heavy physical work during working hours, and moderate leisure-time physical activity and vigorous leisure-time physical activity were categorized as moderate/vigorous activity (≥4 MET). The total time reported per 24-hours was calculated by adding the hours from all the questions in PAS2, we added or subtracted time that was not accounted for to the category light physical activity (2 MET), similar to previous studies (11).

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed by the Graded Cycling Test with Talk Test (GCT-TT), a submaximal aerobic exercise test performed on a stationary bicycle (Monark 928E-G3, Vansbro, Sweden). The outcome of the test was exercise intensity expressed as Watts (W). The GCT-TT identifies the exercise intensity at which the patient perceives that it is no longer possible to speak comfortably due to excessive breathing. The workload was increased by 15 W each minute, and at the end of each minute, the patient recited a standardised text passage. The test was stopped when the patient was no longer able to speak comfortably. A detailed test protocol has previously been published (13), and the test showed high reliability and only minor

measurement errors in patients with ischemic heart disease (14), and in patients with lacunar stroke (13).

Blood pressure and BMI

We measured blood pressure using an automatic blood pressure monitor (Microlife® BP A100/ Microlife® BP A3L Comfort, Widnau, Switzerland) after an overnight fast with the patient in a supine position.

BMI (body weight/height^2 [kilograms/meter^2]) was measured using a body composition monitor (OMRON HBF-500-E; Kyoto, Japan).

Biomarkers

We drew venous blood for assessment of triglycerides, total cholesterol, low-density lipoproteins (LDL) and high-density lipoproteins (HDL) as well as routine analysis.

Other data collection

The following data were collected from patients or patient records: age, sex, mobility, family status, occupation, education level, age, type and location of infarct, hypertension and hypercholesterolemia upon admission, pre-existing diabetes, smoking, and drinking habits.

Statistical analyses

Descriptive statistics were used to characterize the study population, report post-stroke health profile in patients with lacunar stroke and to evaluate whether patients adhered to the recommendations on physical activity for health. Data are presented as mean ± standard deviation (SD) unless otherwise indicated.

To evaluate the association between pre-stroke physical activity level (moderate/vigorous-intensity activity) and risk factors for stroke: sex, age, education, pre-existing diabetes, previous history of hypertension, total cholesterol, LDL, and BMI a multiple linear regression analysis was performed. We also evaluated the association between GCT-TT power output and risk factors for stroke. All tests were two-tailed at a significance level of $p \leq 0.05$. Statistical analyses were performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics version 22 (Armonk, NY, USA).

RESULTS

Baseline characteristics

In total 129 eligible patients with lacunar stroke were identified, 58 patients (45%) declined participation: 25 patients with no reason, 21 due to reduced mental surplus, 8 due to pain and 4 because of work obligations. Of the declining patients, 31 were men (mean age 70±9 years) and 27 were women (mean age 69±11 years). During the physical examination visit, one patient did not complete the cardiorespiratory fitness test due to fatigue of the paretic leg, and two LDL samples were not available for technical reasons related to a high level of triglyceride.

A total of 71 patients with lacunar stroke were included in the study with a mean of 6±4 days (range 1–17) after hospital admission for stroke. The majority (73%) were men, and the mean age for all patients were 64±9 years (**Table 1**).

Physical activity, pre-stroke

Self-reported data on pre-stroke physical activity (PAS2) showed that 56 patients (79%) adhered to the international minimum recommendations on physical activity to improve health, whereas 15 (21%) did not (**Figure 1**). Overall, patients who did not adhere to the recommendations on physical activity did not differ significantly from patients who did adhere in terms of baseline characteristics (**Table 2**). The 56 patients who adhered to the recommendations engaged in a mean of 1 hour and 30 minutes per day in a combination of moderate-intensity and vigorous-intensity activity, while the 15 patients who did not adhere to the recommendations engaged in a mean of 7 minutes per day of moderate-intensity activity and did not perform vigorous-intensity activity at all. In total 25 (35%) patients performed vigorous-intensity activity for a mean of 2 hours and 53 minutes/week.

The total study population reported that, pre-stroke, they slept mean 7 hours and 21 minutes ± 1 hour and 9 minutes per day (range 4–12 hours), engaged in sedentary behaviour: mean 6 hours and 11 minutes±2 hours and 33 minutes per day (range 2–15 hours), engaged in light activity: mean 9 hours and 16 minutes±2 hours and 34 minutes per day (range 1 hour and 26 minutes to 14 hours and 30 minutes) and engaged in moderate/vigorous-intensity activity for a mean: 1 hour and 11 minutes±1 hour and 8 minutes per day (range 0–5 hours). The wide range of hours spent on each activity demonstrates individual differences among the patients (**Figure 2A-B)**.

Hours not accounted for by patient self-report (residual activity) were categorized as light activity, these hours comprised approximately 75% of all light activity.

The total study population had a mean 24-hour MET score pre-stroke of 39±5 METs. The 56 patients who adhered to the recommendations had a mean 24-hour MET score of 41±5 METs while the 15 patients who did not adhere to the recommendation had a mean score of 35±2 METs.

Associations between pre-stroke physical activity and stroke risk factors

The potential interaction of GCT-TT power output and self-reported physical activity, respectively, with risk factors for recurrent stroke (**Table 3**) was analysed by multiple linear regression. When controlling for lifestyle and stroke risk factors, sex was a significant predictor for GCT-TT power output: men's power output was 49W higher than women's ($p < 0.05$). Likewise, when controlling for modifiable risk factors for stroke, there was a significant association between PAS2 (moderate/vigorous-intensity activity pre-stroke) and previous history of hypertension: patients without a previous history of hypertension reported doing 5 hours and 42 minutes/week more of moderate/vigorous-intensity activity pre-stroke than patients with a previous history of hypertension. There was no significant correlation between self-reported pre-stroke physical activity level and age or measured GCT-TT power output.

DISCUSSION

We found that the majority (79%) of our study population adhered to the international minimum recommendations on physical activity to improve health pre-stroke. Though active, only 35% (25 patients) of the total patient population reported vigorous-intensity activity. The baseline characteristics of patients who did not adhere to the recommendations (15 patients) did not differ significantly from those who were active. Of note, self-reported physical activity assessed by PAS2 did not correlate with the objective measure of cardiorespiratory fitness, the GCT-TT.

Similar to the present results, a health survey of the Danish general population from 2017 (15) included questions on time spent doing moderate-intensity and vigorous-intensity activity during an average week, as well as time spent in sedentary behaviour during an average day. The survey showed that 71% of the Danish population, including those >16 years of age, met the international minimum recommendations on physical activity, with higher activity in younger age and men being more active than women. Surprisingly, our study supports these

data in a stroke population, though we saw no age or gender difference in adherence to exercise (Table 2), except for those adhering to both moderate-intensity and vigorous-intensity activity where an overrepresentation of men were seen. These results call for further investigations into the activity required to reduce risk of lacunar stroke, or whether physical activity is of less importance in lacunar stroke compared with other stroke subtypes.

The international recommendations on weekly physical activity to improve health specify the minimum number of hours of exercise required to reduce risk of lifestyle-associated disease (2). For additional health benefits, individuals are encouraged to double the time spent on moderate-intensity activity (300 minutes) or vigorous-intensity activity (150 minutes) or an equivalent combination of both, weekly (2). In this study we also saw a considerable variation of individual adherence among the patients who fulfil the recommendations on physical activity, and a difference in moderate/vigorous-intensity activity between the groups who adhered and those who did not adhere to the recommendations (**Figure 2A-B**). Literature shows that physical activity, including cardiorespiratory fitness, helps reduce the risk of hypertension, cardiovascular disease, and stroke (16, 17). A greater health benefit appears to occur with longer duration, higher frequency and/or higher intensity of activity (17), and a direct dose-response relation is shown between higher duration, frequency, volume, and intensity of activity and reduced risk of coronary heart disease and cardiovascular disease (16, 17).

Patients with symptoms of minor stroke (not classified according to TOAST-criteria) or transient ischemic attack (TIA) show a 5.8–11.7% risk of recurrent TIA or stroke within the first 90 days after stroke onset (18, 19). Thus, early intervention related to modifiable risk factors, such as physical activity may be important to initiate early post-stroke (20). The INTERSTROKE-study, an international case-control study investigating 10 potentially modifiable risk factors associated with stroke, found that physical inactivity was one of the major modifiable risk factors for stroke (1).

In contrast to our hypothesis, many patients in this study adhered to the international recommendations on physical activity, although they mainly reported moderate-intensity activity rather than vigorous-intensity activity. Previous research on cardiac rehabilitation suggests that regular exercise with an intensity level of 13–15 on Borg´s scale of exertion (21)

(corresponding to >6 METs) is needed to obtain positive effects on secondary prevention (22). It is unknown if this also applies to patients with a history of stroke (5). Previous literature suggest that: 1) a high level of physical activity is associated with decreased risk of first-ever stroke (23), 2) physical activity reduces stroke risk factors in the general population (24), and 3) physical activity reduces stroke severity and improves long-term outcomes (2 years) following the first-ever stroke (25). Of note, no studies show that increased physical activity in patients with a history of stroke reduces the risk of recurrent stroke (5). Further research is warranted to determine the "dose" (e.g., type, duration, frequency, intensity, volume) of physical activity necessary to provide the most optimal health benefits for patients with a history of stroke. Nevertheless, even a small move from the category of "no activity" to "some level" of activity may be effective (2).

Though the study population adhered to the recommendations on physical activity pre-stroke, this effort was not reflected in the objective cardiorespiratory fitness measure, the GCT-TT power output. Our study population had a similar GCT-TT power output (mean 114.3±49.7 W) compared with patients with ischemic heart disease (mean 104.3±30.4 W) (26), but there was no direct correlation between PAS2-score and GCT-TT power output. The patients included in this study showed a similar GCT-TT power output as that of patients included in our previous reliability study of GCT-TT in lacunar stroke (13). In the test/re-test reliability study, we included both inpatients and outpatients with lacunar stroke and found a mean GCT-TT power output of 114.8±37.0 W in the first test and 114.0±35.6 W in the re-test (13). Thus, our study population had a similar GCT-TT power output compared with patients 3 months after lacunar stroke.

The apparent lack of association between pre-stroke physical activity and GCT-TT power output may be related to the use of subjective versus objective outcome measures. Objective measures are typically more accurate, as demonstrated in the reliability study of GCT-TT in patients with lacunar stroke (inter class correlation: 0.97 [0.95-0.98]) (13). The subjective measure, PAS2, tends to overestimate the intensity of activity in healthy adults (27).

This study has certain limitations that should be considered when interpreting the results. Firstly, there is a potential for selection bias as patients included in this study were participants in a randomized controlled trial where patients were randomized to 3 month high-intensity

interval training or usual treatment, this may attract patients who are already more physical active than an unselected population of patients with lacunar stroke. Secondly, including only patients with lacunar stroke who tend to be younger (28) than the stroke population in general, may limit the generalisability of the results to other categories of stroke patients. Also, many of the recruited patients were men, which may limit the generalisability. However, the sex difference seen in this study reflects the higher stroke incidence in younger men compared to aged-matched women (29). Additionally, as reported in a validation study on PAS in healthy individuals (27), our patients showed difficulties in recalling the time spent on sedentary behaviour and light-intensity activity, as the total number of hours reported in the PAS2 rarely added up to 24 hours. This may skew the results towards underreporting minor activity. Similarly, it was found that healthy individuals typically recall the duration of physical activity but overestimate the intensity of the activity (27). This could account for part of the discrepancy between self-reported physical activity and our objective measure of cardiorespiratory fitness. The same study also found a trend towards overestimation of physical activity in 24-hour MET-score when using PAS2 (27). Thus, use of self-report questionnaires may introduce recall bias and lead to overestimation of volume as well as intensity of physical activity, and the surprisingly positive result of the present study may represent an optimistic estimate of pre-stroke physical activity.

CONCLUSION

Contrary to our hypothesis, most of the patients (≈ 80 %) in the present study exhibited self-reported pre-stroke physical activity in agreement with or exceeding the international recommendations on physical activity for health. However, only one in three patients reported that they engaged in any vigorous-intensity activity prior to their stroke, and the average cardiorespiratory fitness level of the patients was only slightly better compared to patients with ischemic heart disease from the same geographical area. Studies on the potential beneficial effect of exercise as a secondary prevention strategy to individuals with lacunar stroke with a special emphasis on vigorous-intensity activity are warranted.

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AUTHOR CONTRIBUTIONS

All the authors contributed to the study conception and design. RSK and CK contributed to obtain funding. RSK, AV and CK drafted the manuscript. All authors reviewed the manuscript, provided comments and revisions as well as read and approved the final manuscript.

COMPETING INTERESTS

There are no conflicts of interest.

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TABLES

Characteristics	Patients (n=71)
Men, n (%)	52 (73)
Age, years (mean ± SD) [range]	64±9 [42–80]
Mobility	
Without walking aids, n (%)	63 (89)
Pre-stroke use of walking aids, n (%)	1 (1)
Family status	
Cohabitates, n (%)	47 (66)
Lives alone, n (%)	24 (34)
Occupation	
Working full-time, n (%)	33 (47)
Retired, n (%)	36 (51)
Student, n (%)	1 (1)
Unemployed, n (%)	1 (1)
Education	
Primary education, n (%)	5 (7)
Apprenticeship, n (%)	20 (28)
Upper secondary education/high school, n (%)	3 (4)
Short-cycle tertiary education, n (%)	9 (13)
Bachelors or equivalent, n (%)	17 (24)
Masters, equivalent or higher, n (%)	17 (24)
Sequelae of lacunar stroke, n (%)	7 (10)
Previous clinical symptoms, n (%)	14 (20)
Thrombolysis, n (%)	7 (10)
Clinical symptoms on admission	
Paresis/dexterity of extremities, n (%)	48 (68)
Sensory impairments of the extremities, n (%)	26 (37)
Facial palsy, n (%)	22 (31)
Dysarthria, n (%)	18 (25)
Vertigo, n (%)	15 (21)
Visual problems, n (%)	7 (10)

Table 1. Patient characteristics of the total study population

Characteristics	Adhered (n=56)	Did Not Adhere (n=15)
Men, n (%)	41 (73)	11 (73)
Retired, n (%)	27 (48)	9 (60)
Age, years (mean ± SD)	64.0±8.9	63.0±10.5
GCT-TT, W (mean ± SD)	118.4±50.3♦	99.0±46.0
BMI, kg/m^2 (mean ± SD)	26.4±4.1	27.5±3.9
Total cholesterol, mmol/L (mean ± SD)	5.5±1.4	5.2±1.1
LDL, mmol/L (mean ± SD)	3.2±1.1♣	2.9±1.1

Table 2. Characteristics of the patients who did or did not adhere to the recommendations on physical activity for health, pre-stroke[a,b]

[a]Recommendations on physical activity for health: Moderate-intensity activity ≥150 minutes/week, vigorous-intensity activity ≥ 75 minutes/week or an equivalent combination

[b]None of the values in Table 2 were statistically significant.

♦ n=55

♣n=54

Risk factors	Numbers/ average scores
Hypertension at hospitalization, n (%)	58 (82)
Hypertension known from previously, n (%)	35 (49)
Hypercholesterolemia at hospitalization, n (%)	65 (92)
Pre-existing diabetes, n (%)	8 (11)
BMI, kg/m^2 (mean ± SD)	27±4
Smoking	
Current smokers, n (%)	15 (21)
Previous smokers, n (%)	34 (48)
Non-smokers, n (%)	22 (31)
Alcohol consumption*	
< Health authorities recommendations, n (%)	44 (62)
> Health authorities recommendations, n (%)	27 (38)
Biomarkers	
Total cholesterol, mmol/L (mean ± SD)	5.5±1.3
Low-density lipoproteins**, mmol/L (mean ± SD)	3.1±1.1
High-density lipoproteins, mmol/L (mean ± SD)	1.4±0.4
Triglyceride, mmol/L, (mean, range)	1.6 (0.7-15.5)
Blood pressure	
Systolic pressure, mmHg (mean ± SD)	148±21
Diastoloc pressure, mmHg (mean ± SD)	88±11
Infarct, age	
Acute/subacute infarct, n (%)	64 (90)
First-time stroke, n (%)	38 (54)
Recurrent stroke, n (%)	6 (8)
Only older infarct verified on MRI, with clinical symptoms, n (%)	7 (10)
First-time stroke but also sequela stroke verified on MRI, n (%)	20 (28)
Infarct localisation	
Right hemisphere, n (%)	41 (58)
Left hemisphere, n (%)	27 (38)
Bilateral, n (%)	3 (4)

Table 3. Post-stroke health profile in terms of cardiovascular risk factors.
*The Danish Health authority recommend < 7 units per week for women (1 unit equals 1 glass of wine) and for men < 14 units per week (30). **n=69

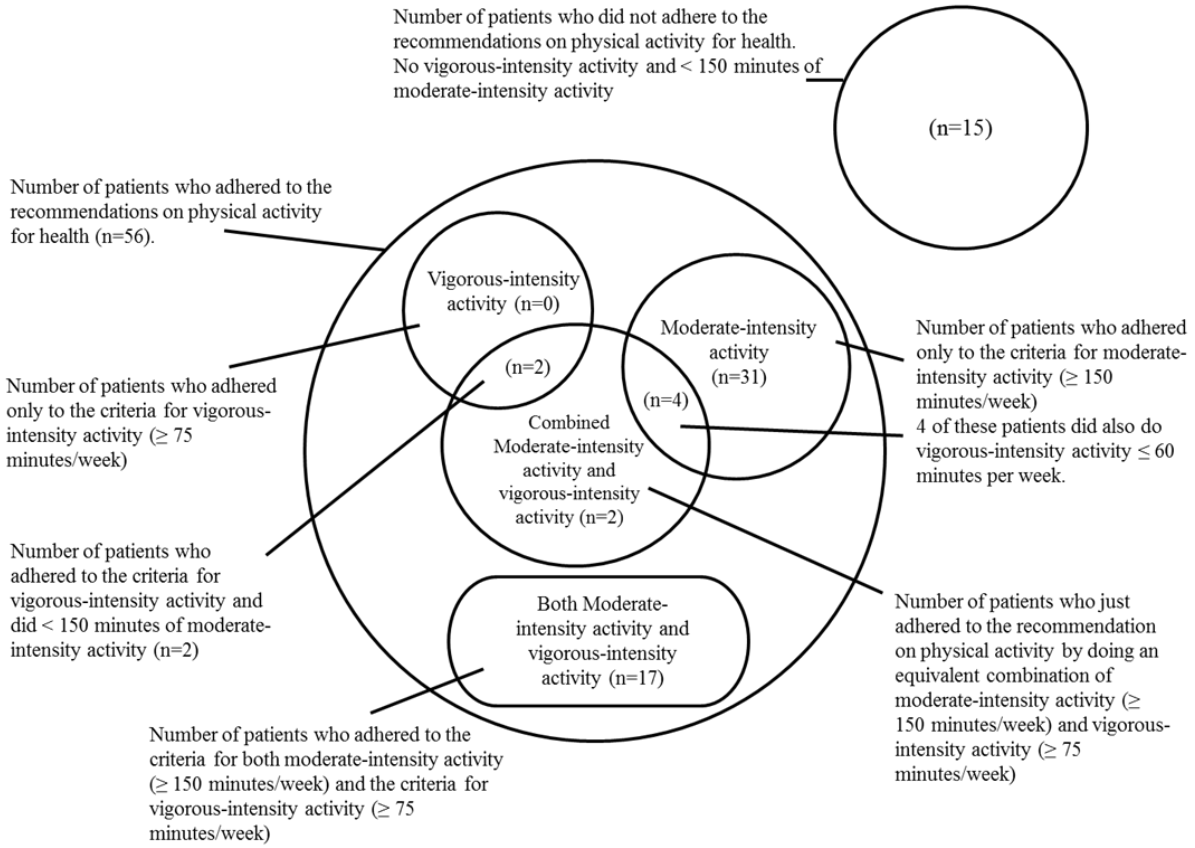

Figure 1. Number of patients and their self-reported engagement in physical activity, pre-stroke.
A total of 56 patients adhered to the recommendations on physical activity for health by performing either moderate-intensity activity (≥150 minutes/week), vigorous-intensity activity (≥75 minutes/week) or an equivalent combination.

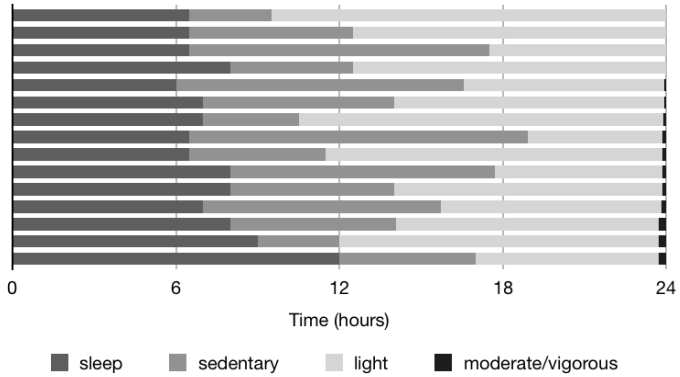

Figure 2A. Patients not adhering to the recommendations on physical activity, pre-stroke (n=15)

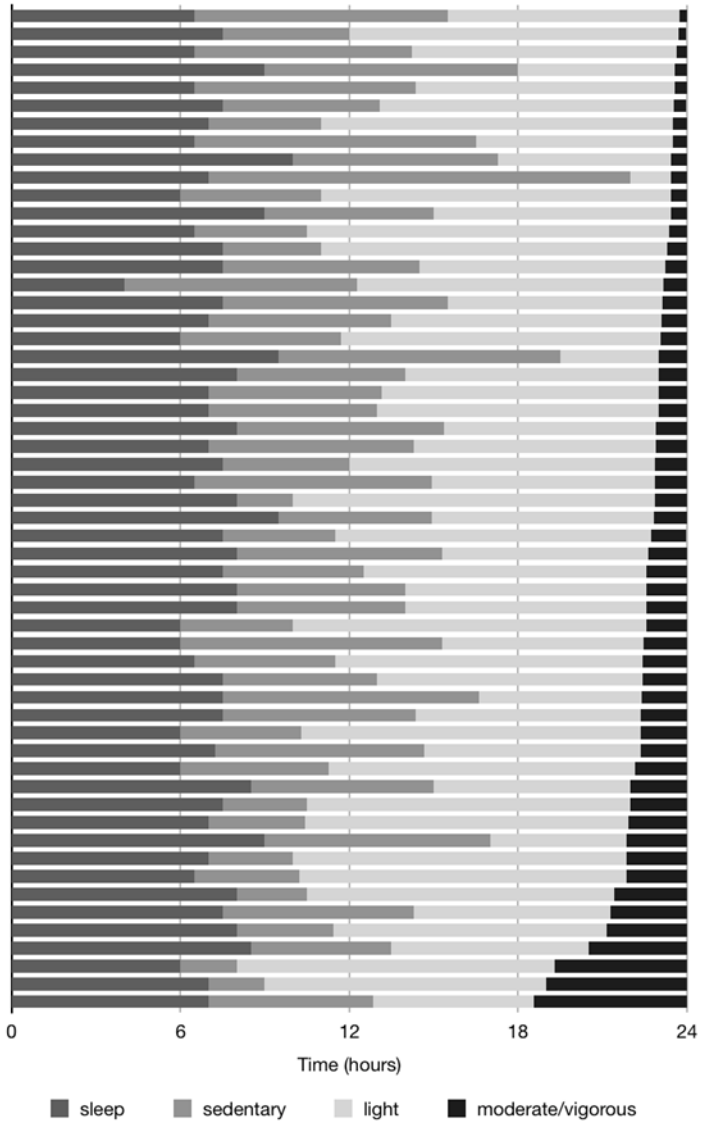

Figure 2B. Patients adhering to the recommendations on physical activity, pre-stroke (n=56)

Figure 2A-B. Overview of 24-hours physical activity profile, pre-stroke.
Figure 2A presents the patients who do not adhere to the recommendations on physical activity and figure 2B presents the patients who adhere to the recommendations. For both figures, each horizontal line represents one individual patient (n=71) and the patients are arranged by ascending time of moderate/vigorous-intensity activity. Figure 2B shows a considerable variation of individual adherence among the patients who adhered.

Effect of Home-Based High-Intensity Interval Training in Patients with Lacunar Stroke: A Randomised Controlled Trial

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ABSTRACT

Background

High-intensity interval training (HIIT) is superior to moderate-intensity continuous training in improving cardiorespiratory fitness in patients with cardiovascular disease, but is it safe, feasible and effective in patients with stroke? The aim was to investigate feasibility and effect of early home-based HIIT in patients with lacunar stroke combined with usual care versus usual care, only.

Methods

In a 1:1 ratio patients were randomized to HIIT or usual care in a randomised controlled trial. We measured the following outcomes at baseline and post-intervention: cardiorespiratory fitness monitored as power output from the Graded Cycling Test with Talk Test (GCT-TT; primary outcome), physical activity, fatigue, depression, well-being, stress, cognition, endothelial function, blood pressure, body mass index, and biomarkers. The study was registered at: (URL: https://clinicaltrials.gov, ID: NCT02731235)

Results

We included 71 patients (mean age 63.7±9.2) 49 men, 31 in intervention group. Home-based HIIT was feasible with no reported adverse events. No significant change between the groups in GCT-TT power output was detected (p=0.90). The change in time spent on vigorous-intensity activity was 2 hours/week and 0.6 hours/week, intervention and usual care respectively (p=0.045). There were no significant differences between groups in the remaining secondary outcomes.

Conclusion

HIIT was feasible and safe in patients with lacunar stroke. Patients can engage early in home-based HIIT when involved in choosing exercise modality and guided by weekly motivational phone calls. Within three months, HIIT did, however, not yield effect on cardiorespiratory fitness. We await further evaluation of long-term effect of this intervention on continued regular physical exercise and cardiovascular event.

Keywords: aerobic exercise, high-intensity interval training, home-based physical activity, secondary stroke prevention, lacunar stroke

Introduction

Stroke is one of the leading causes of mortality and disability (1). Approximately 90% of strokes are attributed to modifiable risk factors, and 75% of the global stroke burden may be avoided by control of behavioural and metabolic risk factors (2). In stroke survivors, lifestyle modifications combined with preventive medication are recommended to be initiated early, as there is a 3.7–6.7% risk of recurrence within the first 90 days after stroke onset (3, 4). The international multicentre study INTERSTROKE (5) highlighted ten common modifiable risk factors associated with ischemic stroke and identified physical inactivity as one of the most important. Several studies have shown that physical activity has a protective effect against stroke (6, 7), as physical activity has the potential to improve cardiorespiratory fitness and reduces blood pressure, lipids, and body weight, thus improving cardiovascular health (8, 9). Physical activity and stroke risk factors can evoke changes in inflammatory, endothelial and cardiovascular biomarkers, which may be used to monitor risk factor load, disease progression or effect of specific interventions (10). Increasing the physical activity, including increasing the frequency, volume, and intensity of exercise, is associated with health benefits (11) and decreased risk of a future stroke in healthy individuals (12-14). Whether this effect also applies to risk of a recurrent stroke in patients with a manifest cerebrovascular event has yet to be fully established (15).

Following stroke, a low level of physical activity (16) and aerobic exercise (17) is often reported, perhaps due to specific barriers to physical activity after stroke. The most frequently reported barriers are environmental barriers, such as challenges in ambulation and transport to the required training facilities, and personal barriers, including lack of motivation and knowledge on how to initiate and maintain an exercise program. Some patients also indicate a fear of recurrent stroke with increased exercise (18, 19). A poorer outcome of early initiated intensive mobilisation has pushed this concern further forward (20).

High-intensity interval training (HIIT) is an exercise modality that could be feasible in patients with stroke due to the low time commitment involved. HIIT has been shown to be a powerful alternative to moderate-intensity continuous training (MICE) to improve cardiorespiratory fitness in cardiac rehabilitation (21). In addition, improved endothelial function after HIIT compared with MICE has also been reported based on flow-mediated dilation of the brachial artery in patients with cardiovascular disease (22). Based on these studies, we hypothesized that a HIIT programme designed to overcome the typical barriers for physical activity in stroke patients is feasible and could improve cardiorespiratory fitness, participation in physical activity, endothelial function, and quality of life in

patients with lacunar stroke. We aimed to investigate the effect of early initiated HIIT for 12 weeks post-stroke in addition to usual care compared with the effects of usual care only.

Methods

Study design

We designed a randomised controlled trial with a parallel-group design. Patients were randomised at a 1:1 ratio to either intervention or usual care, within three weeks of a stroke. Following randomisation, patients were followed for 3 months. The reporting of this study adheres to the CONSORT statement (23).

Ethical approval

The trial was approved by The Danish Data Protection Agency (ID: HGH-2015-021) and the Research Ethics Committee in the Capital Region of Denmark (Trial Registration number: H-15012371). Eligible patients provided written informed consent prior to study participation. Furthermore, the study was registered at URL: ClinicalTrials.gov (ID: NCT02731235, registered January 2016).

Recruitment

Patients were recruited from January 2016 until January 2018 from the stroke unit at hospitals in the Capital Region of Copenhagen, Denmark; Herlev Gentofte Hospital, Rigshospitalet Glostrup, and Nordsjællands Hospital. All assessments were carried out at the stroke unit at Herlev Gentofte Hospital. During the recruitment period, medical records were screened daily by the study coordinator to identify patients with lacunar stroke. Eligible patients were enrolled consecutively within 21 days of stroke onset.

Participants

Patients 18 years or older diagnosed with a first-time lacunar stroke or a recurrent event of lacunar stroke were enrolled in the study. A lacunar stroke was defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST-criteria) (24). This definition included patients with clinical symptoms with a verified relevant brain stem or subcortical hemispheric lesion (<2 cm in diameter in the acute phase) based on computed tomography (CT scan) or magnetic resonance imaging (MRI

scan) (25). Additionally, the patients had a severity of neurological symptoms, categorized as "mild" on the Scandinavian Stroke Scale (SSS) (43-58 points) (26). Patients had to speak and read Danish and provide informed consent. We excluded patients with previous large-artery stroke, unstable cardiac condition, atrial fibrillation, pacemaker, uncontrolled hypertension, diabetes, artery stenosis >50 %, symptoms or comorbidities not allowing exercise on a stationary bicycle, dyspnoea caused by heart or pulmonary disease, aphasia, or dementia that interfered with understanding the protocol and physical examinations.

Procedures

During hospital admission all patients had routine examination for stroke cause and risk factors. These tests included a chest x-ray, 48-hours cardiac event monitoring (Novacor, Rueil Malmaison, France), carotid artery imaging (ultrasound), and routine blood tests (full blood count, glucose, electrolytes, lipids, creatinine, etc.). Furthermore, an MRI (sequences: diffusion-weighted imaging, the derived apparent diffusion coefficient value, fluid attenuated inversion recovery, and T2*-weighted images on a 1.5 T clinical system using an 8-channel standard head coil) (Achieva, Philips Healthcare, Best, The Netherlands) was acquired to confirm diagnosis, localisation, and presence of acute and old ischemic lesions and microbleeds.

All patients complied with medication in accordance with their stroke physicians' recommendation during admission. In addition, all patients were offered usual occupational therapy and physiotherapy during their hospital stay when needed. As part of the usual care procedure, patients were also offered a follow-up visit at the outpatient clinic.

During the trial, we made three study amendments to increase the recruitment rate: 1) we extended the study to include patients with transient ischemic attack (TIA) and previous lacunar stroke (previously only patients with acute/subacute stroke were included), 2) we included patients within 21 days after onset of symptoms (previously only included patients within 7 days), and 3) we expanded the number of recruitments sites to three stroke units in the Capital Region of Copenhagen (previously only one stroke unit was included).

Randomisation and blinding

After completing all assessments at baseline, the patients were randomised into one of two groups: usual care and exercise intervention or usual care only. The randomisation procedure was based on equal allocation with randomly varying block size. The block-randomisation was computer-generated

(8 blocks of 10, mixed with 5 blocks of 4) and carried out by a research assistant not involved in the study. Sealed opaque envelopes were made by the research assistant, stored, and administrated by health personnel not involved in the study. The outcome assessor, data analysts, and study coordinator were all blinded to the randomisation process. Immediately following baseline assessments, the study coordinator collected the next envelope from the health personnel. The consecutively enrolled patient opened the envelope and was allocated to either intervention group or usual care group.

Intervention

Both intervention and usual care group

At baseline, all patients attended a motivational talk with the study coordinator to encourage lifestyle changes, and they were introduced to an exercise catalogue with a range of suggestions for modes of aerobic exercise (e.g. brisk walking stair stepping, stationary bicycling, outdoor cycling, running, indoor rowing, high knee exercises, and swimming).

Intervention group

In addition to usual care, the intervention group performed home-based HIIT daily 3x3 minutes with 2 minutes of active recovery, 5 days per week for 12 weeks (27) (**Figure S1**). HIIT was defined as exercise at 77-93% of the maximum heart rate, corresponding to 14–16 on the Borg-rated perceived-exertion scale (28) or "not able to speak comfortably" on the Talk Test (29-31). The Talk Test determined the initial intensity of the intervention, and the patients progressed the work load and the cadence as they improved throughout the exercise program. In each session, the patients were encouraged to reach an exercise intensity at which they were no longer able to speak comfortably. To determine their speaking comfort the intervention group carried a pocket-sized, laminated standardized text passage (cue card), which became redundant as they got familiar with the text. They also wore a stop watch to time the exercise intervals. The exercise modality was self-chosen assuming it was performed at high intensity. Patients in the intervention group were provided with a stationary bicycle if required (Kilberry® Magnetic Bike JC-950, Proteus Sports Inc., Linkou Township, Taiwan) for use at home to ensure an easily accessible exercise modality. Before initiating the exercise program, the study coordinator visited each patient at home to introduce the exercise program, including the use of the Talk Test. During the exercise period, the study coordinator called the patients on a weekly basis to ensure compliance. Furthermore, the exercise sessions were tracked by the patients in an exercise diary to encourage adherence to the exercise program.

Usual care group

The usual care group received secondary preventive medication and advice on self-managed lifestyle changes. Furthermore, the usual care group was asked to resume their habitual level of physical activity and to track their physical activity in an exercise diary.

Outcome measures

All outcome measures were obtained at baseline and post-intervention, (three months after initiation of the intervention) (**Figure S2**).

Cardiorespiratory fitness

The primary outcome, the Graded Cycling Test with Talk Test (GCT-TT), measured sub-maximal cardiorespiratory fitness monitored as power output in Watts (W). GCT-TT was performed on a stationary bicycle (Monark 928E-G3, Vansbro, Sweden) and identified the exercise intensity at which the patient perceived that it was no longer possible to speak comfortably due to excessive breathing. The workload was increased by 15W every minute, and each minute the patient also recited a standardised text passage (32). When the patient was no longer able to speak comfortably the test terminated. A detailed test protocol has previously been published (33) establishing the feasibility and measurement error for groups (12.9W [standard error of measurement (SEM_{95})]) and for individuals with lacunar stroke (18.3W [smallest real difference (SRD)]) (33). The SRD corresponded to two steps (30W) in the GCT protocol, which represents a change for an individual patient (33).

Post-stroke fatigue

Post-stroke fatigue was measured by the Multidimensional Fatigue Inventory (MFI-20), a generic self-report instrument covering five domains of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue (34). We used a cut-off score ≥12 points in the general fatigue-score as a measure of overall fatigue, as proposed in the original development of the scale (34). Higher score indicated higher degree of fatigue (34).

Depression

Depression severity was assessed by the Major Depression Inventory (MDI). The questionnaire consisted of 12 questions on mood-related symptoms during the previous two weeks, with responses provided on a 6-point Likert scale. The total score ranked from 0–50 points. A high score indicated

more severe depression (35), a score greater than 20 points indicated mild depression, and a score between 15 and 20 points was interpreted as incipient depression (36).

Mental well-being

Mental well-being was measured by the generic World Health Organisation-Five Well-being Index (WHO-5) questionnaire (37). WHO-5 included five positive statements with responses given on a 6-point Likert scale, which corresponded to the patient's own experience for the previous two weeks. The total score ranked from 0–100 points and 50 points indicated reduced well-being or long-term stress (38). In prior studies, the Danish population showed an average score of 69 points (37).

Chronic stress

Chronic stress was evaluated using an algometer (Ull-Meter®, Ull Care, Hellerup, Denmark) with corresponding recording of pain threshold on the sternum, expressed as pressure pain sensitivity (PPS) (39, 40). With the patient in a supine position, the most sensitive point on the sternum was identified, and the hand-held algometer was applied to the sternum with gradually increasing intensity until the pain threshold was reached. The algometer automatically transformed the pain threshold into a logarithmic scale of sensitivity from 30–100 PPS units, with a cut-off ≥60 correlating with markers of a stress syndrome (41). The reading on the algometer was blinded to the observer until completion of the assessment (39, 40).

Cognition

We screened for mild cognitive impairments using the Montreal Cognitive Assessment (MoCA), including the following nine cognitive domains: attention, concentration, executive functions, memory, language, visuospatial ability, conceptual thinking, calculations, and orientation. The total score ranked from 0–30 points, where a score ≥26 points was considered normal cognition (42). MoCA was previously shown to be valid and reliable in patients with lacunar stroke or white matter lesions (43).

Endothelial function and arterial stiffness

Endothelial function was assessed by digital plethysmography to determine the peripheral arterial tonometry using EndoPAT2000 (Itamar Medical Ltd., Caesarea, Israel) and registered as the reactive

hyperaemia index (RHI). An RHI score >1.67 was recommended as a cut-off for normal endothelial function in the user manual of the EndoPAT2000 device.

Arterial stiffness was registered as the augmentation index (AI), together with the heart-rate-corrected AI at a heart rate of 75 beats per min (AI@75). Lower scores indicate greater elasticity of the arteries. Endothelial function and arterial stiffness were both calculated using the EndoPAT software package version 3.4.4. All measures were conducted in accordance with conditions described by the manufacturer, and a detailed procedure has previously been described (44).

Blood pressure

Baseline blood pressure was measured at each visit after an overnight fast, following 5 min of rest with the patient in a supine position using an automatic blood pressure monitor (Microlife® BP A100/ Microlife® BP A3L Comfort, Widnau, Switzerland). We aimed for a blood pressure <130/90 mmHg as recommended for patients with a recent lacunar stroke or TIA (45).

Biomarkers

Venous blood was drawn to assess biomarkers associated with cardiovascular and endothelial function, and inflammation. The cardiovascular biomarkers (pro-adrenomedullin [Pro-ADM], pro-atrial natriuretic peptide [Pro-ANP], and copeptin) are biomarkers to regulate the vascular tone and blood pressure (46, 47). The inflammatory biomarkers (interleukin-6 [IL-6] and tumour necrosis factor [TNF]), and endothelial biomarkers (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1], vascular endothelial growth factor [VEGF], and E-selectin) supplemented the endothelial function data retrieved from EndoPAT. Blood was centrifuged at 4000 rpm for 15 minutes at 4^{o}C within 45 minutes after sampling and all samples were stored at -80^{o}C until analysis. Inflammatory biomarkers and endothelial biomarkers were analysed using commercially available kits from Mesoscale, Rockville, USA (V-PLEX Plus human: IL-6 kit, TNF kit, ICAM-1 kit, VCAM-1 kit, VEGF kit, and E-selectin kit) according to the manufacturer´s instructions. Samples were analysed in duplicate. Prior to measurement, the samples were diluted two-fold in Diluent 41, and MSD Discovery Workbench software was used for analysis (48). The cardiovascular biomarkers were analysed using commercially available kits and software from BRAHMS GmbH Hennigsdorf, Germany (KRYPTOR compact PLUS human: Pro-ADM kit, Pro-ANP kit, and copeptin kit) according to the manufacturer´s instructions. Fasting plasma insulin concentration (49) was

determined using a commercially available kit (ELISA kit, DRG Instruments GmbH, Marburg, Germany) according to the manufacturer's instructions.

Body mass index

Body mass index (BMI) was calculated based on height as measured in centimetres and body weight as measured in kilograms (body weight/height^2) using a body composition monitor (OMRON HBF-500-E; Kyoto, Japan). Obesity was defined by a BMI $\geq$30 kg/m^2 and was associated with increased risk of cardiovascular disease and first-time stroke (45).

Physical activity

We evaluated physical activity both subjectively using the self-reported questionnaire Physical Activity Scale version 2.1 (PAS2) (50) and objectively using an accelerometer (AX3, Axivity, York, UK). In PAS2, patients reported their average physical activity behaviour two weeks prior to hospital admission (baseline) and two weeks prior to the post-intervention assessment. PAS2 revealed daily time spent on sleep, sitting down at work, standing/walking at work, heavy physical work during working hours, active commuting to/from work, and sedentary behaviour, including television watching and reading. Additionally, in PAS2, patients recorded the weekly time spent on light-intensity, moderate-intensity, and vigorous-intensity activity during leisure time (50). Each activity corresponded to a specific MET (metabolic equivalent of task) intensity according to the Compendium of Physical Activity (51), which allows physical activity to be calculated as a total 24-hour MET score. To estimate the average duration of activity per day, each score from the three leisure-time activities was divided by seven. Total time reported per day spent on the activities was calculated by adding the hours spent on all activities. If the total time reported was below or above 24 hours, we added or subtracted time that was not accounted for to the category "light activity," as suggested in a previous study (50).

Objective physical activity was acquired by a wireless three-axis accelerometer (AX3, Axivity, York, UK) fixed with double-sided adhesive tape (VIP Tape, Skinlock International, Charleroi, Belgium) anteriorly on the right medial thigh with a water-resistant patch (Fixomull® transparent, BSN Medical, Inc., Hamburg, Germany). The AX3 was programmed to record activity patterns for 8 days and 7 nights with a frequency of 25 Hz, using manufacturer´s software (Open Movement v.1.0.0.28). After download, data were analysed with Acti4, a custom-made script in MATLAB (version: R2013a),

including a previous described algorithm (52) to identify everyday physical activity types, such as walking, running, cycling, walking stairs, standing up, and sitting down.

Other data collection

The following data were collected from the patients or from patient records: age, sex, clinical symptoms at time of hospital admission, age, type and location of the lesion, mobility, family status, occupation, education level, pre-existing diabetes, hypertension and hypercholesterolemia upon hospital admission, and smoking and drinking habits.

Statistical analyses

Sample size

Sample size calculation was based on the primary outcome (GCT-TT power output). Using a two-tailed 5% level of significance and a power of 80%, to detect a minimal clinical important average difference of 23 W, a sample size of 84 patients (42 in each group) was needed. With allowance for a dropout rate of 15%, we aimed to enrol 100 patients in total.

No prior studies have established a minimal clinical important difference for the GCT-TT power output. The decision to choose a 23W average difference was based on a previous study in cardiac patients (53) reporting that the smallest detectable average change for a group of patients (SEM_{95}) was 18.3W and the smallest real difference for an individual patient (SRD) was 25.9W (corresponding to two 15W-steps in the incremental test protocol). An average difference for a group of patients clearly exceeding 23W are closer to two incremental steps (30W) than to one (15W) incremental step in the test protocol. Thus, it was our best estimate of a minimal clinical important average difference between groups.

Analysis

We analysed complete outcome data according to the group the patients were randomised to, regardless of patient compliance. All available data for each patient were included in the analysis. Missing data were not imputed. Data on demographics and baseline characteristics were compared between the groups using independent *t*-test for comparison of means and Fisher´s exact test for comparison of proportions.

To evaluate outcome changes between the groups for both the primary outcome and for secondary outcomes, we used analysis of covariance (ANCOVA) for continuous variables, the Mann-Whitney test for ordinal variables (estimating the difference at the post-intervention assessment), and Fisher´s exact test for proportions. For evaluation of differences within each treatment group for both primary and secondary outcomes, we used a paired *t*-test for continuous variables and a Wilcoxon signed rank test for ordinal variables. The differences, both between groups and within groups, were calculated and given as mean difference with 95% confidence intervals (CI). Before analysis, all variables were tested for normal distribution using histograms and QQ-plots, and if necessary, the data were logarithmically transformed. All data were analysed with a two-tailed test and with a statistical significance level set at $p<0.05$. Data were analysed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics 22 (Armonk, NY, USA). Statistical planning and analysis were conducted in cooperation with one of the authors, a biostatistician (TWK).

Results

No significant differences were found between the groups in terms of demographics or baseline characteristics (**Table 1**), and no adverse events were recorded during the study.

Study recruitment

We screened records on all patients admitted to the stroke unit (n=3,098) daily and excluded 2,969 patients who did not have a diagnosis of lacunar stroke. A total of 58 patients with lacunar stroke declined participation due to the following reasons: reduced mental surplus (n=21), no reason given (n=25), pain (n=8), and work obligations (n=4). Of the declining patients, 31 were men (mean age 70±9 years) and 27 women (mean age 69±11 years). In total, 71 patients with lacunar stroke were included with a mean symptom severity score (SSS score) on admission of 55±5 points. The first assessment visit took place 12±7 days post hospital admission.

Between March 2016 and April 2018, 63 patients attended the post-intervention assessment. Eight patients (11%), four in each group, were lost to the post-intervention assessment due to chronic pain, work obligations, hospitalization, or reduced mental surplus, and some withdrew their consent without cause (**Figure 1**). The patients lost to the post-intervention assessment had a mean age of 63±11 years, five were women, and six lived alone. Of the 63 patients included in the analysis, five

patients (8%) were re-admitted to the hospital for observation of TIA within the first 3 months after lacunar stroke (one patient from the intervention group and four from the usual care group).
The study was terminated as planned, but due to low recruitment, we did not fulfil the intended inclusion number, and extension of inclusion was not possible due to time and finances.

Primary outcome

In total, 58 patients were analysed with the GCT-TT at the post-intervention assessment. Three patients from the usual care group did not complete the GCT-TT due to fatigue of the paretic leg on the day of examination, worsening of knee pain from bilateral knee osteoarthritis, and technical problems with the bicycle. Two patients from the intervention group did not complete the GCT-TT due to either nausea, dizziness, and stomach ache on the day of examination or acute low back pain (**Figure 1**).

There was no significant difference over time between groups in GCT-TT power output (p=0.90; **Table 2**). However, 17 of 29 patients in the intervention group improved their GCT-TT power output from baseline to post-intervention assessment, and 11 of 29 patients in the usual care group improved their GCT-TT power output from baseline to the post-intervention assessment (p>0.05; data not shown). Eight patients in each group improved ≥30W in GCT-TT power output, and this change corresponded to two steps in the GCT-TT protocol, equivalent to a clinically relevant change.

Secondary outcomes

Physical activity

At baseline, 21 patients in the intervention group and 18 patients in the usual care group reported that they did not spend time on vigorous-intensity activity. We found a significant behavioural change in time spent on vigorous-intensity activity (PAS2) in the intervention group compared with the usual care group from baseline to the post-intervention assessment (p=0.045; **Table2**).
In the intervention group, 18 patients increased (58 %), 6 patients decreased (19 %), and 7 patients (23 %) did not change their participation in vigorous-intensity activity. In the usual care group 9 patients (28 %) increased, 7 patients decreased (22 %), and 16 patients (50 %) did not change their participation in vigorous-intensity activity **(Figure 2)**. A higher proportion of patients in the intervention group increased their participation in vigorous-intensity activity from baseline to the post-intervention assessment (p=0.01).

In the intervention group, 15 of 21 patients (71 %) and 5 of 18 patients in the usual care group (28 %) went from, not participating in vigorous-intensity activity at baseline to participate in any vigorous-intensity activity at the post-intervention assessment. Furthermore, we found that more patients both from the intervention group and the usual care group performed more physical exercise at the post-intervention assessment compared to baseline. The most substantial positive change was seen for the intervention group regarding their increase in vigorous-intensity activity (**Figure 3**).

General well-being and Cardiovascular function

No change was detected between groups in the level of post-stroke fatigue, chronic stress, depression, mental well-being, cognition, blood pressure or endothelial function (**Table 2**).

Biomarkers

Statistically significant reductions in lipids were observed within both groups (p=0.00, p=0.00, respectively) (**Table 3**). Fasting insulin was reduced in both groups over time, however the decrease in the usual care group was marginally reduced compared to the intervention group (p=0.048). A significant reduction in ICAM-1 in the usual care group compared to the intervention group (p=0.006) and VCAM-1 was slightly increased in the intervention group compared to the usual care group (p=0.024) (**Table 3**). The changes were, however, small with no consistent effect on specific functions (inflammation, endothelium and cardiovascular).

Exercise adherence

According to the exercise diaries, patients in the intervention group reported that they, on average, performed the exercise program 56 of 60 days (93%). For reference, 60 days of exercise corresponds to 5 days per week for 12 weeks. In the intervention group, 10 of 31 patients (32%) performed the exercise program more than 5 days per week (>100% adherence), while 24 patients (77%) in the intervention group performed the exercise program ≥4 days per week (≥ 80% adherence).

A total of 23 patients (74%) in the intervention group chose to complete the aerobic exercise sessions on the provided stationary bicycle, whereas the remaining 8 patients performed brisk walking (1 patient), stair stepping in combination with outdoor cycling on different days (2 patients), running (2 patients), brisk walking combined with outdoor cycling on different days (1 patient), brisk walking combined with rehabilitation twice a week in the community (1 patient), and indoor rowing (1 patient).

According to the patients´ exercise diaries, in which they recorded the number of days with any kind of activity during the 12-week study (84 days), the intervention group reported that they were physically active 64±12 days (5.4 days per week), whereas the usual care group reported physical activity on 51±24 days (4.2 days per week). Physical activity, measured objectively with accelerometers, did not show a significant difference within or between the groups from baseline to the post-intervention assessment (**Table 2**).

Discussion

The main findings of this randomised controlled trial on home-based HIIT were that an early initiated HIIT exercise program was feasible and safe in patients with lacunar stroke and that a significant proportion of patients in the intervention group markedly increased their time spent on vigorous-intensity activity compared to patients in the usual care group. This reported increase in physical activity, however, was not translated into an improvement in GCT-TT power output. HIIT did not significantly improve the general well-being (depression, chronic stress, post-stroke fatigue, cognition, and quality of life), cardiovascular function (blood pressure and endothelial function). For biomarker outcomes (cardiovascular, inflammatory, and endothelial) the results were ambiguous with no obvious beneficial effect of HIIT on the endothelial response.

Only a few studies have investigated the effect of HIIT in stroke patients (54), and only three studies were randomised controlled trials (55-57). In the present study, we have investigated HIIT as a home-based intervention with distant supervision for patients with lacunar stroke. HIIT is more often performed as individual treadmill training after stroke to improve mobility, gait speed, and gait stride (54). Only one randomised controlled trial reported a superior effect of HIIT versus MICE to improve cardiorespiratory fitness in patients with stroke (55). More studies that evaluate the effects of the various available exercise methods are needed to confirm these findings. The current study highlights the need for additional research to investigate the effect of HIIT on cardiorespiratory fitness in stroke patients.

The exercise intensity was not monitored during the home-based training and a too low exercise intensity may explain part of the missing cardiovascular effects. We chose not to measure the exercise intensity with heart rate monitors based on clinical observations in a small test of feasibility which showed that the stroke patients were not able to comply with the available monitoring equipment.

Their familiarity with, and ability to use smartphones was not consistent, and some patients developed a skin rash following use of electrocardiography electrodes for more than 3–5 days. Furthermore, the commercially available heart rate monitors at the initiation of the study did not have the required memory capacity or battery life for weeklong monitoring.

Another cause of discrepancy between reported activity and lack of cardiovascular effects may be the relatively short exercise duration (15 minutes of exercise 5 days a week). When planning the study, our hypothesis was that patients with lacunar stroke were likely to be unfamiliar with physical activity and feasibility of the intervention was a main priority. There is no general consensus on the ideal HIIT protocol for motor recovery and improved cardiorespiratory fitness after stroke (58). The most frequently used HIIT protocol in patients with cardiovascular disease targeting endothelial function, was 4x4 minutes, three times per week (22). Additionally, adherence to the international recommendations on physical activity for health require 75 minutes of weekly vigorous-intensity activity (59), thus we chose 15 minutes 5 times a week.

Furthermore, the current home-based HIIT intervention was designed to be easy for patients to perform at home, easy to translate into clinical practice, and at low-cost in an effort to reduce the known barriers for physical activity in stroke survivors (18, 19).

All patients, also those in the usual care group, were aware of being enrolled in an exercise study with regular assessments, and all patients were informed on the importance of physical activity following stroke. These features of the study may have encouraged all patients to be physically active. In addition, the supervision of all patients by a physiotherapist during the baseline assessment of the GCT-TT may have decreased the fear of doing aerobic exercise following stroke also in the usual care group. Despite encouragements and a subtle increase in physical activity, a change exceeding the previously established SEM_{95} of 12.9 W (33) was not observed either within the groups or between the groups in GCT-TT power output.

Patients with an ischemic stroke or a transient ischemic attack (TIA) have an increased risk of recurrent stroke and cardiovascular events (60). Consequently, medical intervention or change in lifestyle factors are often suggested. Secondary prevention using medication is effective in preventing recurrent stroke (45). However, the evidence exploring the effect of lifestyle changes on recurrent stroke is not solid (45). Two recent reviews explored lifestyle interventions, including cardiovascular exercise to prevent cardiovascular events after stroke and TIA (61). They found no effect on

cardiovascular events, but a significant reduction in systolic blood pressure, fasting insulin and fasting glucose, and an increase in high-density lipoprotein cholesterol (61, 62). However, our study was not able to confirm similar significant findings on cardiovascular function.

A priori we were curious to see if we could detect an improvement in general well-being (depression, chronic stress, post-stroke fatigue, cognitive function, and mental well-being) in favour of the intervention group. We did, however not detect a significant improvement between the groups within the first three months of stroke. The few previous studies reporting on the efficacy of exercise (aerobic exercise and resistance training) on depression and well-being showed inconsistent results (63), though a trend towards exercise having a positive impact on cognitive function has been suggested (63). There is not yet sufficient literature available on the efficacy of non-pharmacological interventions to prevent or treat post-stroke fatigue (64), likewise there is a lack of knowledge on the effect of exercise on stress, none of these outcomes were affected in this study, however the baseline values were surprisingly good leaving little room for possible improvement. Of note, the sample size was small, and the effects of HIIT may become more consistent and significant in a larger sample size.

Studies have showed that HIIT had a protective effect on endothelial function in patients with cardiovascular disease (22). Also, aerobic exercise reduces the blood pressure in patients with stroke or TIA (65). Consequently, we expected an improvement on endothelial function in favour of the intervention group, but such was not detected within the three months of exercise. It may be related to a potentially low exercise intensity and to a short daily exercise duration but may also be caused by a low incidence of or too well-managed co-morbidities to decrease endothelial function such as diabetes or hypertension in our patient population.

Based on the literature investigating patients with cardiovascular disease, we primarily expected a decrease in biomarkers following physical exercise. Inflammatory biomarkers (IL-6 and TNF) were shown to decrease in patients with coronary heart disease (10, 66). Endothelial biomarkers, ICAM-1, VCAM-1 (66, 67), VEGF (68, 69) were all shown to decrease in patients with cardiovascular risk factors, whereas there was insufficient evidence on the efficacy of exercise on E-selectin. Cardiovascular biomarkers (pro-ADM, pro-ANP) were shown to decrease in patients with heart failure (70, 71), and limited literature is available on the efficacy of exercise on Copeptin. We found only minor changes in the assessed biomarkers without clinical relevance between the groups. When comparing the baseline values from the included stroke patients to values from healthy individuals

(manufacturer´s normative values), the levels of inflammatory, cardiovascular biomarkers and ICAM-1 were generally higher in the stroke patients. This difference may reflect the underlying cardiovascular risk factors in our patient sample.

During the study period, we found an 8% rate of hospital readmittance for observation of a TIA. These findings are similar to those in previous studies that identified a risk of 3.7–6.7% of hospital readmittance within the first 90 days after stroke (3, 4).

By providing the patients with a stationary bicycle, calling them on a weekly basis and monitoring them at baseline, we succeeded in engaging patients with lacunar stroke into being more physically active, including performing vigorous-intensity activity. These findings are very encouraging compared to the results of a large international multicentre study (ExStroke), which found no effect of repeated encouragement and verbal instructions on physical activity in patients with ischemic stroke (72). In addition, the Look AHEAD study (73) did not show an effect on cardiovascular events when aiming for lifestyle changes. The study investigated weight reduction by eating fewer calories combined with increased physical activity (unsupervised home-based exercise) by using repeated encouragement (individual sessions and group meeting) in patients with type 2 diabetes. In Look AHEAD, half of the study population dropped out or had no change in physical activity. These results highlight the difficulties of encouraging individuals to make lifestyle changes and the challenges in maintaining them.

Strengths and limitations

The tailormade HIIT intervention performed in the patients´ home environment was considered a strength of this study in contrast to supervised group sessions performed on specific days and hours at a designated training facility, which would likely interfere with non-flexible working hours and transportation if the patients are not allowed to drive after stroke. The choice of no supervision and monitoring of the daily exercise intensity was, however, a limitation of the present intervention. Also, only 8 days of physical activity were monitored using accelerometers rather than the entire intervention period. We supplemented the accelerometers with use of self-reported diaries, which may be subject to recall bias and subconsciously encourage the patients to report better performance to meet own expectations or those of the researcher. In this study we failed to recruit the power-estimated predetermined number of patients due to a low recruitment rate. Since no effect of exercise

was detected (p=0.90), it is highly unlikely that a statistically significant difference would have been reached by inclusion of 15 more patients in each group. Recruitment bias may have occurred since patients, who were already interested in physical exercise were probably more likely to participate in a study investigating an exercise intervention. Another point to raise is the sex distribution of the sample as the majority of the included patients were male (78%), which could influence the generalisability of the findings. However, the present sample reflects the general population of patients with stroke quite well – i.e. higher incidence of stroke in younger men compared to aged-matched women (74).

Conclusion

The home-based HIIT protocol in the present study was safe and well received by the patients. The compliance was good leading to increased vigorous-intensity physical activity and training on a daily basis. This increase in physical activity was however not translated into an effect in cardiorespiratory fitness, general well-being, or improvement in biomarkers within the first three months of training. This may be caused by a small sample size, insufficient intensity of exercise or a bias in selection of patient who were already physically active on enrolment. Further studies investigating how this exercise approach can be optimized with special emphasis on monitoring of exercise intensity, and on finding the ideal training volume, are warranted to develop an effective HIIT protocol in patients with lacunar stroke.

Abbreviations

AI	Augmentation index
ANCOVA	Analysis of covariance
BMI	Body mass index
cLDA	Constrained longitudinal data analysis
CT	Computed tomography scan
GCT-TT	Graded Cycling Test with Talk Test
HIIT	High-intensity interval training
ICAM-1	Intercellular adhesion molecule-1
IL-6	Interleukin-6
IQR	Interquartile range
MDI	Major depression inventory
MET	Metabolic equivalent of task
MFI-20	Multidimensional fatigue inventory
MICE	Moderate-intensity continuous training
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
PPS	Pressure pain sensitivity
Pro-ADM	Pro-adrenomedullin

Pro-ANP	Pro-atrial natriuretic peptide
RHI	Reactive hyperaemia index
SD	Standard deviation
SEM_{95}	Standard error of measurement with 95 % certainty
SRD	Smallest real difference
TIA	Transient ischemic attack
TNF	Tumour necrosis factor
TOAST	Trial of Org. 10172 in acute stroke treatment
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

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Author contributions
CK and AV contributed substantial to the study conception and design, supervised and facilitated all work performed at the stroke unit, Herlev Gentofte hospital and provided key intellectual content to the manuscript. CK and RSK obtained funding for the study. RSK contributed substantial to the study conception and design, coordinated, planned and performed the intervention, including the patient assessments, processed data and performed statistical work. The statistical analysis was performed in collaboration with TWK and ER who also provided key content and critically reviewed the manuscript. JF and NCP contributed to the study design, supervised data acquisition and provided key content to the manuscript. HKI and TC contributed to the data acquisition and provided key content to the discussion section and critically reviewed the manuscript. SR and KLL contributed to the data analysis, interpretation of results and critically reviewed the manuscript.
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Declaration of conflicting interests
There are no conflicts of interest.

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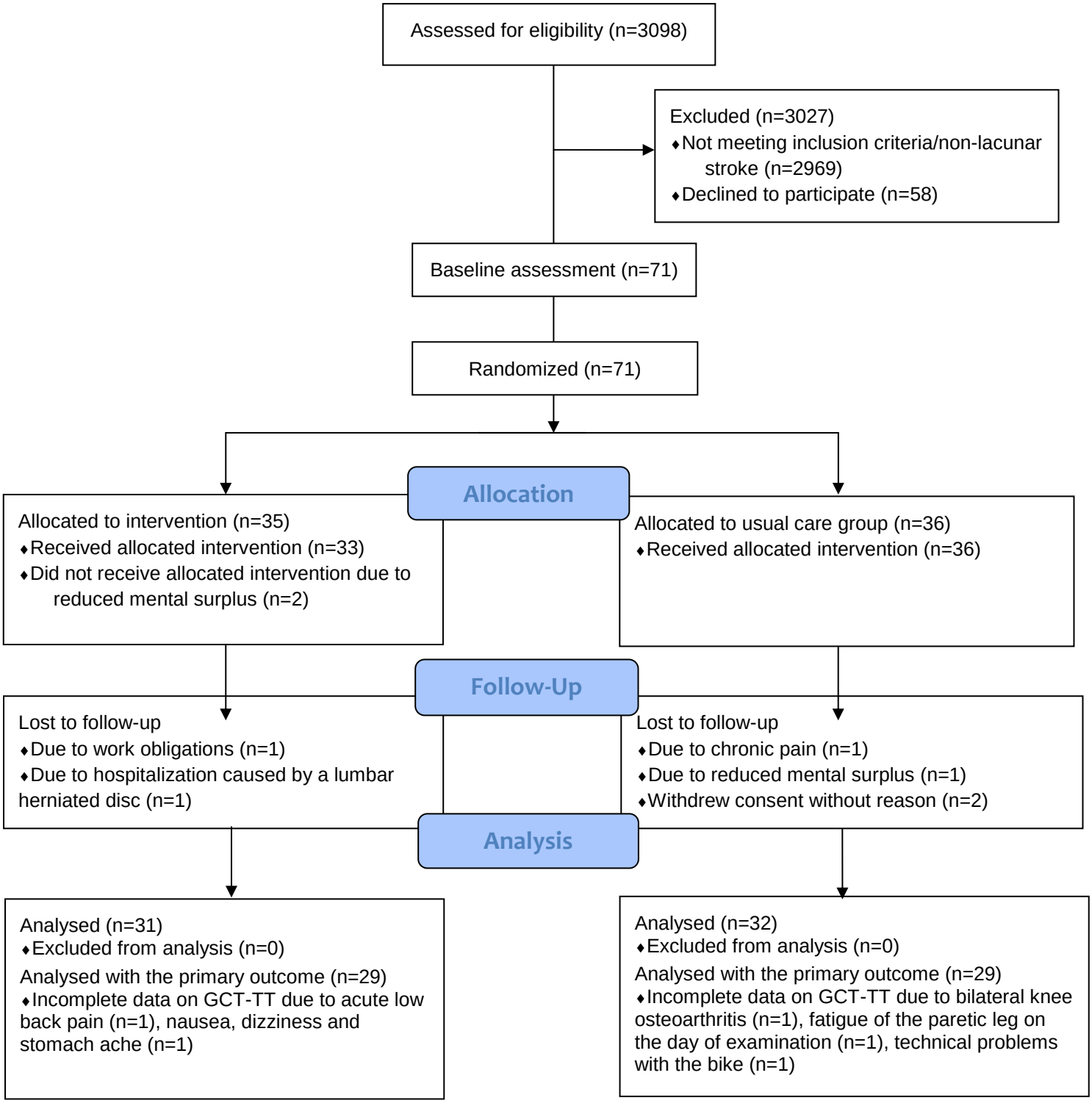
Figure legends

Figure 1. Flow diagram of the randomised controlled trial to investigate effect of home-based HIIT in patients with lacunar stroke

Figure 2. Change in vigorous-intensity activity from baseline to the post-intervention assessment in both groups. The figure shows the number of patients in each group who either increased, did not change or reduced their time spent on vigorous-intensity activity from baseline to post-intervention assessment.

Figure3. Self-reported adherence to physical activity.
Percentages of patients in the intervention group and in the usual care group who adhered or did not adhere to the international recommendations on physical activity at baseline and at the post-intervention assessment. The patients were considered adherent if they performed vigorous-intensity activity (≥75 minutes per week), moderate-intensity activity (≥150 minutes per week), or an equivalent combination. The figure also shows the percentage of patients in the intervention group and in the usual care group who participated in any vigorous-intensity activity at baseline and at the post-intervention assessment.


Assessed for eligibility (n=3098)
Excluded (n=3027)
♦Not meeting inclusion criteria/non-lacunar stroke (n=2969)
♦Declined to participate (n=58)
Baseline assessment (n=71)
Randomized (n=71)
Allocation
Allocated to intervention (n=35)
♦Received allocated intervention (n=33)
♦Did not receive allocated intervention due to reduced mental surplus (n=2)
Allocated to usual care group (n=36)
♦Received allocated intervention (n=36)
Follow-Up
Lost to follow-up
♦Due to work obligations (n=1)
♦Due to hospitalization caused by a lumbar herniated disc (n=1)
Lost to follow-up
♦Due to chronic pain (n=1)
♦Due to reduced mental surplus (n=1)
♦Withdrew consent without reason (n=2)
Analysis
Analysed (n=31)
♦Excluded from analysis (n=0)
Analysed with the primary outcome (n=29)
♦Incomplete data on GCT-TT due to acute low back pain (n=1), nausea, dizziness and stomach ache (n=1)
Analysed (n=32)
♦Excluded from analysis (n=0)
Analysed with the primary outcome (n=29)
♦Incomplete data on GCT-TT due to bilateral knee osteoarthritis (n=1), fatigue of the paretic leg on the day of examination (n=1), technical problems with the bike (n=1)

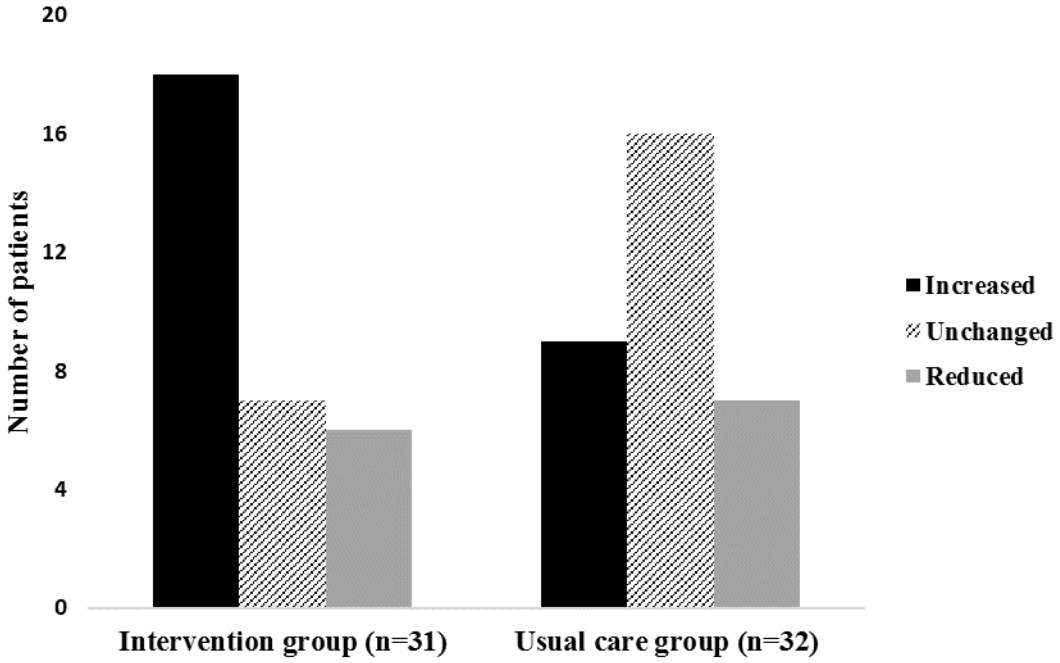


Figure 2. Change in vigorous-intensity activity from baseline to the post-intervention assessment in both groups.

The figure shows the number of patients in each group who either increased, did not change or reduced their time spent on vigorous-intensity activity from baseline to post-intervention assessment.

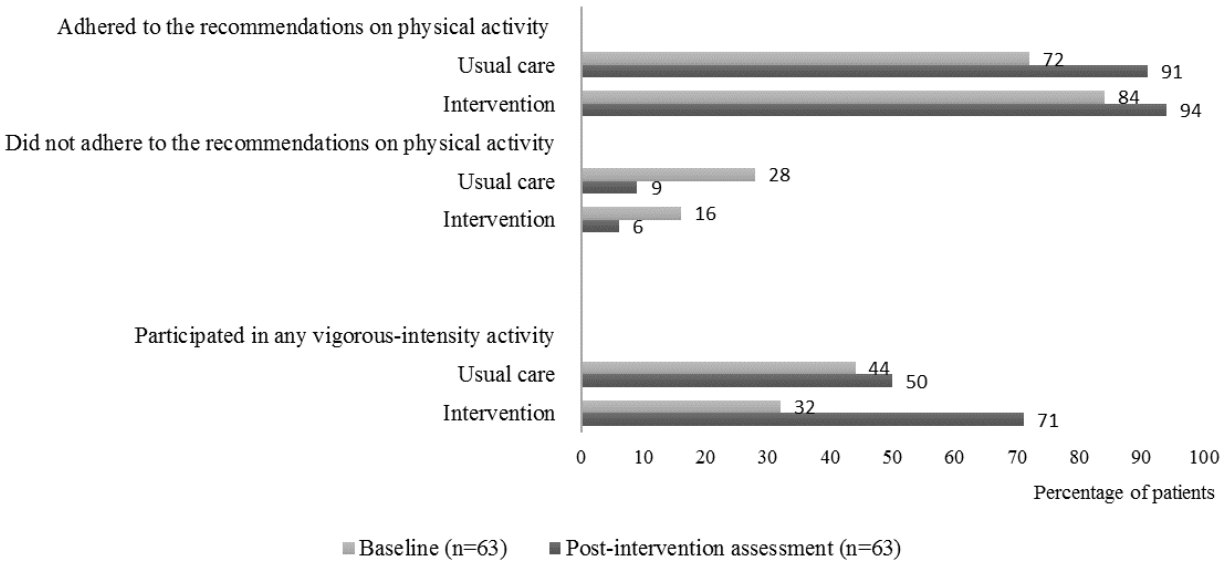


Figure 3. Self-reported adherence to physical activity. Percentages of patients in the intervention group and in the usual care group who adhered or did not adhere to the international recommendations on physical activity at baseline and at the post-intervention assessment. The patients were considered adherent if they performed vigorous-intensity activity (≥75 minutes per week), moderate-intensity activity (≥150 minutes per week), or an equivalent combination. The figure also shows the percentage of patients in the intervention group and in the usual care group who participated in any vigorous-intensity activity at baseline and at the post-intervention assessment.

Variable	Intervention (n=31)	Usual care (n=32)
Men, n (%)	23 (74)	26 (81)
Age, years (mean ± SD)	63.7±8.9	63.7±9.2
Mobility		
Without walking aids, n (%)	28 (90)	30 (94)
Pre-stroke use of walking aids, n (%)	0	1 (3)
Scandinavian stroke scale, points (mean ± SD)	54.6±5.8	55.3±4.4
Family status		
- Cohabitants, n (%)	22 (71)	23 (72)
- Living alone, n (%)	9 (29)	9 (28)
Education		
- Primary education, n (%)	1 (3)	3 (9)
- Apprenticeship, n (%)	9 (29)	9 (28)
- Upper secondary education/high school, n (%)	1 (3)	1 (3)
- Short-cycle tertiary education, n (%)	6 (19)	2 (6)
- Bachelor or equivalent, n (%)	9 (29)	5 (16)
- Masters, equivalent or higher, n (%)	5 (16)	12 (38)
Lesion, age		
- First-time stroke, n (%)	18 (58)	17 (53)
- Recurrent stroke, n (%)	3 (10)	2 (6)
- Only older infarct verified on MRI, with clinical symptoms, n (%)	1 (3)	4 (13)
- First-time stroke but also sequela stroke verified on MRI, n (%)	9 (29)	9 (28)
Acute/subacute infarct, n (%)	30 (97)	28 (88)
Previous clinical symptoms, n (%)	8 (26)	4 (13)
Thrombolysis, n (%)	3 (10)	3 (9)
Hemispheric localisation of lesion		
- Right hemisphere, n (%)	19 (61)	18 (56)
- Left hemisphere, n (%)	12 (39)	12 (38)
- Bilateral, n (%)	0	2 (6)
Lesion localisation		
- Thalamus	9	5
- Basal ganglia	17	19
- Frontal lobe	2	2
- Pons	1	4
- Medulla oblongata	1	1
- Corpus callosum	0	1
- Motor cortex	1	0

Clinical symptoms on admission		
- Paresis/dexterity of extremities, n (%)	23 (74)	18 (56)
- Sensory impairments of the extremities, n (%)	11 (35)	12 (38)
- Facial palsy, n (%)	7 (23)	11 (34)
- Dysarthria, n (%)	6 (19)	11 (34)
- Vertigo, n (%)	5 (16)	8 (25)
- Visual problems, n (%)	5 (16)	2 (6)
Cardiovascular risk factors		
Hypertension at hospitalization, n (%)	26 (84)	25 (78)
Hypertension previously known, n (%)	17 (55)	14 (44)
Pre-existing diabetes, n (%)	3 (10)	2 (6)
BMI, kg/m^2 (mean ± SD)	28±5	26±4
Smoking		
- Current smokers, n (%)	6 (19)	6 (19)
- Previous smokers, n (%)	14 (45)	16 (50)
- Non-smokers, n (%)	11 (36)	10 (31)
Alcohol consumption**		
< health authorities' recommendations, n (%)	18 (58)	21 (66)
> health authorities' recommendations, n (%)	13 (42)	11 (34)
Lipids		
Total cholesterol, mmol/L (mean ± SD)	5.6±1.3	5.5±1.4
LDL, mmol/L (mean ± SD)	3.3±1.3	3.1±1.0♣
HDL, mmol/L (mean ± SD)	1.4±0.5	1.4±0.4
Triglycerides, mmol/L (mean ± SD)	2.0±1.1	1.7±0.8♣
Blood pressure		
Systolic pressure, mmHg (mean ± SD)	149±22	147±21
Diastolic pressure, mmHg (mean ± SD)	85±10	89±11

Table 1. Patient characteristics at baseline.
No significant difference was detected between the groups.
**The Danish Health authority recommends <7 units per week for women (1 unit equals 1 glass of wine) and <14 units per week for men (75).
♣n=30

	Intervention		Usual care		Difference between groups from baseline to post-intervention assessment		
Variable	**Baseline** (n=31)	**Post-intervention assessment** (n=31)	**Baseline** (n=32)	**Post-intervention assessment** (n=32)	**Difference in change**	**95% CI**	***p****
Primary outcome							
♣GCT-TT, W, (mean ± SD)	118.5±43.1	126.2±46.3	119.5±44.0	126.2±47.9	0.90	-13.9-15.7	0.90
Secondary outcomes							
Post-stroke fatigue, points (mean ± SD)	10±5	11±5	11±3	10±4	1.3	-0.4-3.1	0.13
▲Chronic stress, points (mean ± SD)	62±16	59±15	57±16	55±17	0.7	-5.7-7.1	0.83
Depression, median [IQR]	5 [1;10]	6 [3;13]	9 [4;12]	7 [4;15]			0.86†
Mental well-being, points (mean ± SD)	65±23	69±16	64±18	69±17$	-0.6	-7.7-6.5	0.86
Cognition, median [IQR]	27 [27;29]	29 [28;30]$	28 [26;30]	29 [28;30]$			0.37†
Physical activity (PAS2)							
- Physical activity, MET (mean ± SD)	39.7±4.7	39.1±4.8	39.3±4.8	40.5±4.2	-1.6	-3.6-0.3	0.10
- Sleep, hours/week (mean ± SD)	52.4±6.7	55.1±8.3	51.6±9.6	52.1±8.6	2.4	-0.7-5.5	0.10
- Sedentary behaviour, hours/week (mean ± SD)	40.7±15.3	42.1±17.9	44.1±18.2	39.6±17.3$	5.1	-1.1-11.3	0.10
- Light activity, hours/week (mean ± SD)	66.6±16.8	62.3±19.1	63.9±19.2	66.8±19.5	-6.2	-14.1-1.8	0.13
- Moderate activity, hours/week (median [IQR])	6.2 [2.6;10.0]	6.0 [2.0;10.0]	5.5 [2.0;8.9]	6.9 [4.4;10.5]			0.28†
- Vigorous activity, hours/week (median [IQR])	0.0 [0.0;2.0]	2.0 [0.0;3.0]$	0.0 [0.0;2,4]	0.6 [0.0;2.0]			0.045†
•Endothelial function							
- RHI, index (mean ± SD)	2.6±1.0	2.6±0.8	2,3±0.5	2.3±0.5	0.1	-0.2-0.4	0.4
Arterial stiffness							
- AI (% change in peak systolic pulse wave) (median [IQR])	20 [10;34]	24 [5;39]	11 [3;34]	14 [4;34]			0.43†
- AI@75 (% change in peak systolic pulse wave) (median [IQR])	12 [3;25]	19 [-1;25]	2 [-3;29]	7 [-3;27]			0.45†

Blood pressure							
- Systolic, mmHg (mean ± SD)	149±22	144±18	147±21	141±16$^{\$}$	2.5	-4.9-9.7	0.5
- Diastolic, mmHg (mean ± SD)	85±10	83±10	89±11	84±7$^{\$}$	0.5	-3.2-4.1	0.8
BMI, kg/m^2 (mean ± SD)	27.5±4.5	27.4±4.3	25.6±3.6	25.4±3.6$^{\$}$	0.3	-0.1-0.6	0.2
**Objective physical activity (hours/day)							
- Activity (including cycling, climbing stairs, running, and walking), (median [IQR])	0.08 [0;0.38]	0.05 [0;0.5]	0.08 [0;0.66]	0.06 [0;0.6]			0.92†
- Stand/move around, (median [IQR])	1.40 [0.91;2.69]	1.58 [0.89;2.73]	1.63 [1.07;2.79]	1.67 [1;2.69]			0.78†
- Sedentary behaviour (including sitting/lying), (median [IQR])	19.0 [16.9;20.2]	18.9 [17.2;20.6]	18.4 [17.3;19.9]	18.5 [17.1;19.7]			0.62†
- Total steps/day (mean ± SD)	7208±4170	7068±3953	8251±2814	7877±2163			0.8

Table 2 shows results for outcomes measured at baseline and at the post-intervention assessment for both groups.

Difference in change is only provided when a mean difference could be calculated.

IQR: interquartile range, *calculated by ANCOVA, † calculated by Mann-Whitney test (between the groups at the post-intervention assessment), ♣ 29 patients in each group, $^{\$}$ data from within-group analysis are significant, **26 patients in each group, ♦30 patients in each group, ▲ 31 patients in the usual care group.

	Intervention		Usual care		Difference between groups from baseline to post-intervention assessment		
Variable	**Baseline**	**Post-intervention assessment**	**Baseline**	**Post-intervention assessment**	**Difference in change**	**95% CI**	***p****
	(n=31)	(n=31)	(n=32)	(n=32)			
Lipids							
- Total cholesterol, mmol/L (mean ± SD)	5.6±1.3	4.2±0.9[$]	5.5±1.4	4.1±1,2[$]	0.05	-0.4-0.5	0.8
- LDL, mmol/L (mean ± SD)	3.3±1.3	2.1±0.6[$]	3.1±1.0[•]	2.1±0.8[•,$]	-0.03	-0.4-0.3	0.9
- HDL, mmol/L (mean ± SD)	1.4±0.5	1.5±0.5	1.4±0.4	1.4±0.4	0.10	0.00-0.28	0.3
- Triglycerides, mmol/L (mean ± SD	2.1±1.1	1.3±0.6[$]	1.7±0.8[•]	1.2±0.7[•,$]	-0.06	-0.03-0.2	0.6
Blood samples							
Cardiovascular biomarkers							
- Pro-adrenomedullin, nmol/L (median [IQR])	0.57 [0.53;0.71]	0.62 [0.54;0.75][$]	0.58 [0.52;0.64]	0.54 [0.54;0.68]			0.58[†]
- Pro-atrial natriuretic peptide, pmol/L (median [IQR])	64 [50;94]	72 [57;105][$]	71 [51,84]	73 [50;93]			0.40[†]
- Copeptin, pmol/L (median [IQR])	6.5 [4.6;10.2]	6.7 [5.5;10.4]	6.2 [4.6;9.5]	6.7 [4.8;9.7]			0.55[†]
- Insulin pmol/L (median [IQR])	117 [82;166][▲]	106 [82;148][▲]	91 [77;138][•]	87 [65;103] [•,$]			0.048[†]
Inflammatory biomarkers							
- IL-6 pg/ml (median [IQR])	1.40 [0.81;3.12]	1.13 [0.82;1.73][$]	0.83 [0.71;1.17]	1.10 [0.75;1.52]			0.35[†]
- TNF pg/ml (median [IQR])	2.27 [1.88;3.53]	2.48 [1.97;2,74]	2.21 [1.89;2.81]	2.32 [1.86;3.20]			0.43[†]
Endothelial biomarkers							
- ICAM-1 µg/mL (median [IQR])	0.80 [0.64;0.95]	0.78 [0.62;1.26][$]	0.82 [0.59;1.08]	0.68 [0.55;0.82][$]			0.006[†]
- VCAM-1 µg/mL (median [IQR])	1.11 [0.60;1.34]	1.16 [0.77;1.52][$]	1.06 [0.63;1.46]	0.98 [0.61;1.24]			0.024[†]
- VEGF pg/ml (median [IQR])							

	29.8	30.3	31.2	29.8	0.99†
- E-selectin, ng/mL (median	[25.1;41.7]♠	[22.5;42.7] ♠	[25.2;41.2]◊	[21.1;42.8]◊	
[IQR])	6.22	5.54	5.09	4.76	0.34†
	[4.12;9.88]	[4.61;7.48]	[3.60;7.19]	[4.07;6.58]	

Table 3 shows the results for biomarkers measured at baseline and at the post-intervention assessment for both groups.
Difference in change is only provided when a mean difference could be calculated.
IQR: interquartile range, *calculated by ANCOVA, † calculated by Mann-Whitney test (between the groups at the post-intervention assessment), $ data from within-group analysis are significant, ◊n=25, ▲n=28, ♠n=29, •n=30.

Supplementary materials.

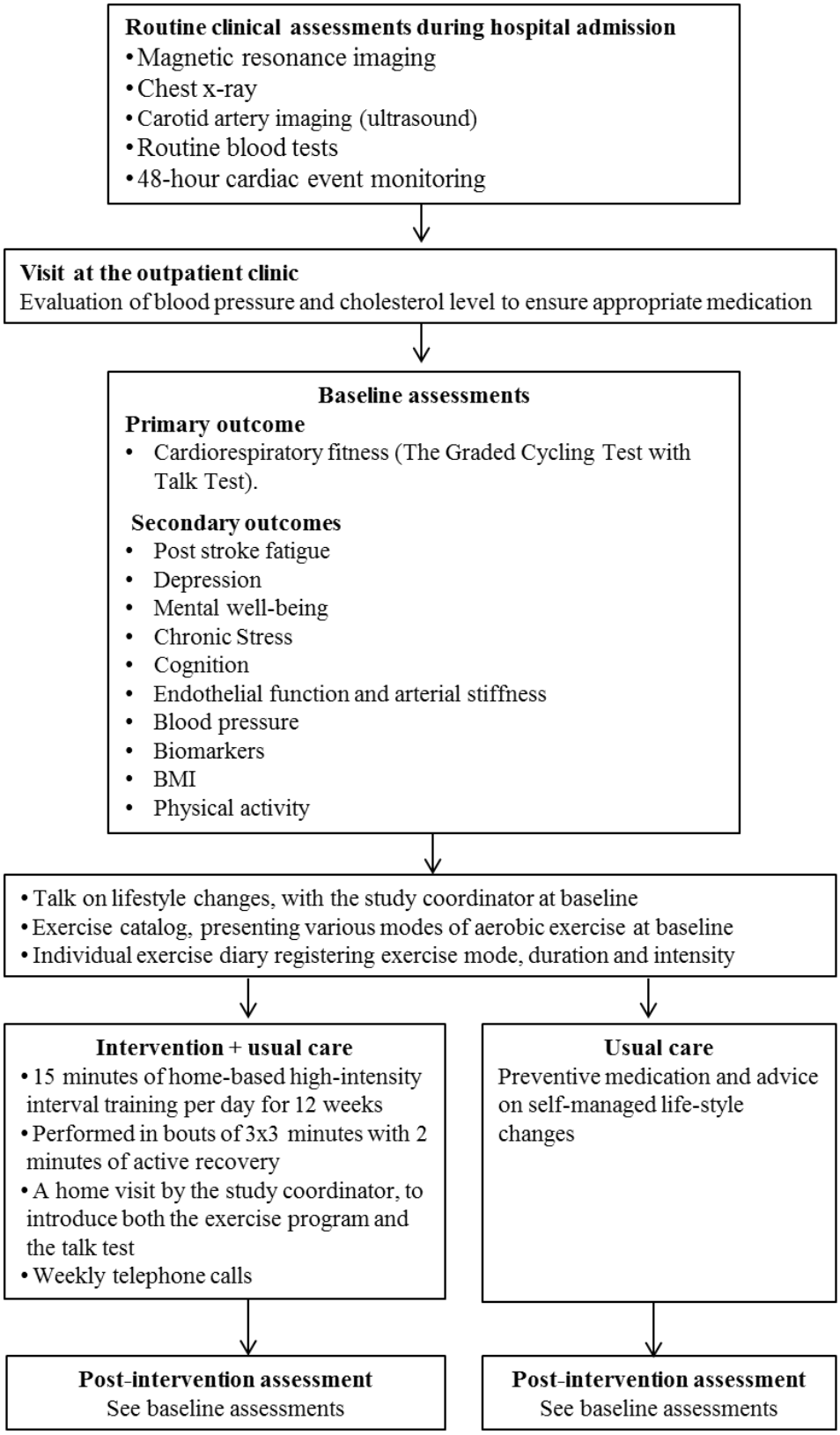


Figure S1. Overview of study procedure

Week no.	**-2**	**-1**	**Baseline assessment**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Post-intervention assessment**	**13**
Cardiorespiratory fitness			X													X	
Post-stroke fatigue			X													X	
Chronic stress			X													X	
Depression			X													X	
Mental well-being			X													X	
Cognition			X													X	
Endothelial function and arterial stiffness			X													X	
Blood pressure			X													X	
Biomarkers			X													X	
BMI			X													X	
AX3, recording 8 days from assessment			→	→												→	→
PAS2, questionnaire returned on assessment visit, reporting average physical activity for the past two weeks	←	←	←											←	←		

Figure S2. Time schedule for study assessments. AX3: an accelerometer measuring activity patterns for everyday physical activity. PAS2: Physical Activity Scale version 2.1 - a self-reported questionnaire of average time spent on everyday physical activity at different intensities.

Appendix

Co-authorship declarations

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DECLARATION OF CO-AUTHORSHIP

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Principal supervisor	Christina Kruuse

Title of PhD thesis:
Effect of early initiated high-intensity exercise in patients with small vessel disease stroke

This declaration concerns the following article:
Graded Cycling Test with Talk Test" Is a Reliable Test to Monitor Cardiovascular Fitness in Patients with Minor Stroke

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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Effect of early initiated high-intensity exercise in patients with small vessel disease stroke

This declaration concerns the following article:
Home-based aerobic exercise in patients with lacunar Stroke: design of the HITPALS randomized controlled trial

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
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GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
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Information on PhD student:	
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Work place	Department of Rehabilitation, Herlev Gentofte University Hospital
Principal supervisor	Christina Kruuse

Title of PhD thesis:
Effect of early initiated high-intensity exercise in patients with small vessel disease stroke

This declaration concerns the following article:
Self-reported physical activity and health profile in patients with small vessel disease stroke: baseline values from the HITPALS-study

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	**(A,B,C)**
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
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C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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Title of PhD thesis:
Effect of early initiated high-intensity exercise in patients with small vessel disease stroke

This declaration concerns the following article:
Short-term follow-up after home-based high-intensity interval training in patients with small vessel disease stroke: a randomized controlled trial

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
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